Anticipatory Nausea and Vomiting in Cancer Chemotherapy Patients at Christchurch Hospital.

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This research is dedicated to the memory of Nicole Megan M^{c}Lauchlan, who died from cancer on the 25th of June, 1990. She will live on in the hearts of everyone who knew her.

"And when your sorrow is comforted (time soothes all sorrows) you will be content that you have known me. You will always be my friend. You will want to laugh with me. And you will sometimes open your window, so, for that pleasure . . . And your friends will be properly astonished to see you laughing as you look up at the sky! Then you will say to them, 'Yes, the stars always make me laugh!'"

From 'The Little Prince', Antoine de Saint-Exupery (1945)

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May you all live long and prosper.

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The primary aims of this study were to assess the prevalence of anticipatory nausea and vomiting in cancer patients who are receiving their chemotherapy in a setting where the new 5-HT_3 receptor antagonists are being used for antiemetic therapy, and to identify any relationships that may exist between the development of anticipatory symptoms and various demographic, clinical and psychological variables.

Twenty-five patients were followed for an average of five chemotherapy cycles, with 24% developing anticipatory nausea and 4% developing anticipatory vomiting. The average severity of the anticipatory nausea was 'very mild' and there was only one episode of 'very mild' anticipatory vomiting. The patients who developed anticipatory nausea and vomiting reported significantly higher levels of state anxiety, trait anxiety, and depression. The difference in self-reported anxiety and depression was more distinct prior to the patients' first three cycles of chemotherapy. Interestingly, the relationship between state anxiety, trait anxiety, and the development of anticipatory nausea revealed that the incidence of anticipatory nausea and vomiting increased as the levels of anxiety and depression decreased. The anticipatory patients also displayed higher expectations of experiencing nausea and vomiting as a side effect of their treatment.

The anticipatory patients were significantly younger than those who did not develop anticipatory symptoms. The anticipatory patients also reported more frequent and severe posttreatment nausea and vomiting.

The results of this study indicate that the prevalence of anticipatory nausea and vomiting remains relatively high despite the introduction of 5-HT_3 receptor antagonists as the primary antiemetic in the Christchurch Hospital Oncology Centre. However, the results suggest that the severity of the anticipatory nausea and vomiting has decreased considerably. The results also provide more support for the classical conditioning model of acquisition. It is proposed that it may be possible to identify patients at risk of developing anticipatory nausea and vomiting, with the opportunity of implementing proven therapeutic strategies which may decrease the incidence of anticipatory symptoms as well as posttreatment nausea and vomiting.

Chapter I

INTRODUCTION

Cancer

Cancer is a disease in which cells escape the factors, still largely unknown, that regulate normal cell growth. As a consequence, the cells multiply out of control - crowding out, invading, and destroying other tissues. Cancer is often considered a group of diseases rather than a single disease because, with few exceptions, any one of the two hundred or more cell types in the human body can become malignant. The behaviour of the cells and the prognosis of the illness depend largely on the type of cells affected.

PREVALENCE

Cancer is a major disease, with high incidence and mortality rates around the world. Every year, more than 15 million people receive a diagnosis of cancer (Bonica, 1979). In 1988 over 160,000 people died from cancer in the UK (Cancer Research Campaign, 1989), and in the USA the figure was around 400,000. Worldwide one out of four or five people will develop some form of cancer in their lifetime (Hirayama et al., 1980). In New Zealand the incidence is relatively high due to our higher than average life-span, with about one quarter of all deaths in New Zealand being cancer related (Abdelaal, 1992). The only cause of death which is greater than cancer in New Zealand is diseases of the heart, which accounts for about one third of all deaths. Lung, colorectal, breast and stomach cancers form the majority of cancer diagnoses. In Europe the leading cause of death in males is lung cancer and the leading cause of death in females is breast cancer (Cancer Research Campaign, 1988). The prevalence of cancer is increasing every year, as we start to live longer and as the our population becomes older.

DIAGNOSIS AND ASSESSMENT

Cancer is usually discovered in one of three ways. Firstly, the patient may have been screened for cancer because he or she is seen as being at risk due to their age, gender or a pre-existing medical condition. The second way in which cancer may be found is when the patient notices an unexplained change in their health, a lump, or a spot on their skin. Also, cancer may be discovered while the patient is being examined for an unrelated reason, such as a general medical checkup or during an operation. When the

cancer is found, it may be the primary cancer (at the site of origin) or it may be a metastasis (a secondary cancer, relatively distant from the primary site).

Usually the general practitioner is the first to detect or suspect cancer; after which, assessment by an appropriate specialist is arranged. For example, if a man has a testicular lump or suspected prostate cancer he will be referred to a urologist, or a woman with a breast lump will most likely see a general surgeon. The specialist may suggest additional tests and will usually arrange for a biopsy or removal of all or part of the cancer. Following the biopsy, the specialist will tell the patient what was found and a plan for further tests and possible treatment is usually discussed. The choices for treatment depend on where the cancer is and on its likely behaviour. Many patients will also see an oncologist, who specialises in the treatment of cancer, and who has trained in radiation and/or chemotherapy treatment.

TREATMENT

Despite the connotations of imminent death which accompany the diagnosis of cancer, on average 46 percent of women and 35 percent of men with cancer in the UK are alive five years after diagnosis (Watson, 1991). At the end of the nineteenth century, surgical excision of a tumour was the mainstay of cancer treatment. In the 1920s and 1930s the advent of radiotherapy greatly increased the options available and more recently the use of chemotherapy has also become a treatment option for many cancers .

Sometimes, major surgery is advised in the hope of removing the cancer entirely. This is usually done after it is confirmed that the removal is technically possible and that there is no evidence of metastases. Other times, a smaller operation is performed, with the hope of removing a majority of the cancer. However, in some cases surgery is not possible or the cancer is so advanced that it offers no advantage with respect to cure, length of survival, or general well-being. Some surgical operations are delayed until the cancer has been reduced in size by either radiotherapy or chemotherapy, so that a smaller, less mutilating operation is possible with a high chance of cure. For other cancers complete surgical removal is not necessary for a cure and the disease is controlled by chemotherapy or radiotherapy.

In New Zealand, about 70% of all patients with cancer have surgery performed on them and in 60% surgery is the sole method of treatment. Radiotherapy is used in about 25% of all patients and chemotherapy in about 15% of all patients receiving cancer treatment, with around half of these receiving radiotherapy or chemotherapy as the sole method of treatment (Abdelaal, 1992).

SUMMARY

A diagnosis of cancer is no longer a death sentence, as the public perception of cancer would have us believe. There are effective treatments available for many forms of this very common disease. With prompt treatment using surgery, radiotherapy, and/or chemotherapy, it is now possible to cure some cancers, provide an extended life-expectancy for others, and improve the quality of life for many more patients.

Chemotherapy

Chemotherapy is the treatment of cancer with drugs which destroy cancer cells. Cancer chemotherapy was first developed after it was noticed that soldiers who had been exposed to mustard gas died soon after from a complete lack of bone marrow. Consequently, it was discovered that the mustard gas affected rapidly dividing cells. So, as cancer cells are rapidly dividing by nature there was a concentration of interest in trying to modify the mustard gas into a form which could be given to cancer patients. From this came the development of the Nitrogen Mustards, including Mustine which is still in use today.

Chemotherapy has an advantage over other treatment modalities in that it is systemic; and since the drugs circulate through the whole body, the anatomical site of the tumour is less important. Chemotherapy is therefore one of the principal treatments for the relatively small population of diseases which are always disseminated (leukemia for example), usually disseminated (for example, many lymphomas), usually disseminated by the time they are diagnosed (for example, small cell lung cancer), or which are disseminated by the time they are diagnosed.

Specific diseases which may be definitively treated by chemotherapy, using chemotherapy as the sole treatment modality, are: Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphatic leukaemia, acute myeloid leukaemia, hairy cell leukaemia, testicular teratoma (including seminoma), ovarian teratoma, choriocarcinoma, and some childhood tumours. Types of cancer in which chemotherapy may be used as neo-adjuvant treatment, where the chemotherapy is used to reduce the size of bulky tumours so that they may be removed or irradiated more easily, are: Squamous carcinomas of the head and neck, transitional cell carcinoma of the bladder, bulky mediastinal Hodgkin's disease, and some childhood tumours. Diseases in which adjuvant chemotherapy has been found to be useful, where the chemotherapy is given after the tumour has been removed in order to control distant metastases, are breast cancer and ovarian cancer. Diseases in which salvage chemotherapy may be needed, where the initial disease was treated and has relapsed, are stage I and II Hodgkin's disease and testicular seminoma. Diseases in which palliative chemotherapy frequently produces significant

improvements in survival and/or quality of life are ovarian cancer, breast cancer, and small cell lung cancer (Calvert & McElwain, 1988). About 10% of all patients treated with chemotherapy are cured, about 40% respond to the chemotherapy but are not cured, and the remaining 50% do not respond to their chemotherapy (Watson, 1991).

THE PROCESS OF RECEIVING CHEMOTHERAPY

Chemotherapeutic drugs may be given in any of several different ways, depending upon the dose, the preferences of the medical staff and the patient, and the type of cancer. The drugs may be introduced into the body: orally (PO) - pills, capsules, or liquids taken by mouth; intravenously (IV) - injection into a vein, either fast (IV push) or slow (IV drip or infusion); intramuscularly (IM) - injected into a muscle; subcutaneously (SC) - injected underneath the skin; intra-arterially (IA) - injected into an artery; intrathecally (IT) - injected into the spinal fluid; intracavitarily (IC) - injected into the pleural cavity of the chest or into the abdomen; or topically - applied directly to the skin, in the mouth, or into the vagina. Most often chemotherapy is given either orally or intravenously, with many protocols combining both methods. Chemotherapy is most often injected into veins in the lower arm or hand because they are usually the most accessible and convenient, although sometimes these veins are not viable and other areas are needed for access. For protocols which involve frequent intravenous infusions a 'portacath' is sometimes used, involving the placement of a permanent indwelling catheter into a major blood vessel.

Most intensive chemotherapy regimens, predominantly involving intravenous administration, are administered on one day every three or four weeks, although some protocols require fortnightly administration (e.g. ABVD) or even weekly treatment (e.g. 5-FU). Some protocols take only a few minutes to administer, such as the weekly 5-FU component for the treatment of colon cancer used in this study, whereas other protocols require three or four hours for administration, such as the fortnightly doses of adriamycin, bleomycin, vinblastine, and dacarbazine for the treatment of Hodgkin's Disease. Most chemotherapy is currently given on an outpatient basis, with inpatient

chemotherapy reserved for the most toxic regimens (usually those containing cisplatin) or for those patients who are considered to be too unwell to be at home.

MODE OF ACTION AND SIDE EFFECTS

The chemotherapy drugs in use today work either by chemically interfering with DNA replication at the early stage of cell division or by interfering with protein synthesis. Both modes of action impede cell division at a very basic level. Not all cancer cells respond to chemotherapy. This may be because only a small percentage of the cancer cells are actively dividing and therefore susceptible to chemotherapy. Cancers with a large percentage of dividing cells are usually particularly responsive to chemotherapy. For example, both cancer of the testes and acute leukaemias generally have a high proportion of actively dividing cells and both are potentially curable by chemotherapy, even when widespread.

Some cancers are resistant irrespective of the proportion of dividing cells. The malignant cells within a cancer may differ in their ability to respond to drugs. Given chemotherapy, the sensitive cells will respond but the resistant cells will slowly proliferate and this will result in the progressing cancer being predominantly made up of resistant cells.

Any rapidly dividing cell population is susceptible to the effects of chemotherapy, necessarily resulting in losses to normal cell populations. Consequently, following the administration of the chemotherapy there is a temporary halt in production of blood cells in the bone marrow, making the patients susceptible to infection, anaemia, and bruising more easily. The cells of the mouth and gut are also affected, resulting in mouth and gut ulceration in some cases. Loss of hair and retardation of nail growth are also common.

Another major side effect of most chemotherapy regimens is nausea and vomiting, both acutely (immediately following administration) and in many cases delayed (defined as 24+ hours after administration).

Normal cells usually recover from chemotherapy using inbuilt repair mechanisms, whereas cancer cells are generally more primitive and often lack this ability. Therefore, chemotherapy is given in repeated doses at time intervals just long enough to allow

adequate recovery of normal cells but which causes an ongoing reduction in the number of cancer cells. This is usually around three to four weeks and is usually judged from recovery of the blood cell count.

No two people experience exactly the same side effects in response to the same drugs (Bruning, 1985). Some side effects for some drugs are very common, such as alopecia (hair loss) with adriamycin, while other side effects are quite rare. Some side effects may be only temporary or intermittent; or they may persist for the duration of the treatment, linger after the treatment as a memory, or never go away completely. They may be severe or slight, serious or minor, annoying or devastating. It is usually impossible to say exactly when side effects will occur and how long they will last. For example, nausea and vomiting, extreme tiredness or weakness, dizziness, diarrhoea, and constipation typically last a few hours to a few days and then disappear; although sometimes one or more of these side effects may persist for some time.

REDUCTION OF CHEMOTHERAPY SIDE EFFECTS

Side effects can be kept to a minimum by carefully adjusting the dose of the chemotherapy drugs as well as other drugs, such as antiemetics and sedatives. A lot has been done in the last ten years to make the side effects easier to bear, but to a certain degree the side effects depend upon the attitude and overall health of the patient. A positive attitude, full of hope and confidence, can make side effects less noticeable and more tolerable. Also, a strong, healthy, young body may withstand the rigours of some drugs better than a weakened or older one.

Nausea and vomiting are managed using a variety of antiemetic drugs prescribed to suit individual requirements. The availability and use of antiemetics will be discussed in much greater detail in a later section.

Wigs are often provided before hair loss occurs and normal hair growth usually resumes after the treatment is over. Some chemotherapy drugs do not cause hair loss.

Psychological support may be required in circumstances where the side effects of treatment have been excessive. This may involve instruction in more appropriate coping strategies, providing emotional support, introducing the patient to other cancer patients

in the same situation, or the use of some of the behavioural treatments discussed in more detail later.

LONG-TERM SIDE EFFECTS OF CHEMOTHERAPY

Due to the way in which some chemotherapy agents interact with and bond to cellular DNA, they may lead to adverse effects months or years after treatment.

Some drugs cause infertility and others may temporarily decrease production of ova and sperm, and recovery may take months or years. Some women go on to an early menopause. Adequate contraception is important during chemotherapy because of uncertainty at any given time whether the patient is fertile or not. Chemotherapy drugs may, but not always, have some effects on the developing foetus. Sperm banking is sometimes an option for young men likely to be rendered infertile by curative chemotherapy.

Another problem is the development of a second, new cancer. Very intensive chemotherapy, particularly with certain drugs, places the patient at greater risk of developing a new malignancy. This risk may be slightly increased if radiation treatment is also given. However, the risk is still much less than the risk of recurrence of the first cancer, or of death had the first cancer not been successfully treated. It is especially important to consider this risk when planning for curative treatment.

CHEMOTHERAPY DRUGS

There are approximately twenty drugs commonly used in the treatment of cancers today, although fewer than ten are used very often. They are usually classified according to their chemistry and the way in which they act on cancer cells.

Better responses are gained from the use of combinations of three or four drugs and where possible, drugs with different toxicities are chosen. However, drugs may exhibit different side effects when given in combination.

Recently there has been a focus on the development of slightly modified forms of older drugs (analogues) which retain the activity of the parent drug but which have fewer side effects.

Drug Emetogenicity

No chemotherapy drug causes nausea and vomiting in every patient it is administered to. In an effort to assess how emetogenic the chemotherapy protocols used on the patients in this study are, a 'Chemotherapy Drug Toxicity' questionnaire (Appendix 1) was constructed and circulated throughout the oncology department at Christchurch Hospital. Twelve questionnaires were completed by the medical staff, who had, on average, been working in oncology for more than nine years. The results of this questionnaire were compared to other reports on the emetogenicity of chemotherapy drugs.

Table 1 shows how the medical staff of the oncology department at Christchurch Hospital rated the individual drugs used in the protocols of the patients in this study; including the perceived frequency with which the chemotherapy drugs induce nausea and/or vomiting and the perceived severity of the nausea and/or vomiting which they induce. The most emetogenic drugs are at the top of the table and the least emetogenic drugs are nearest the bottom.

Cisplatin is the drug perceived to be the most emetogenic and is believed to almost always cause severe nausea and/or vomiting. All other reports on the emetogenicity of chemotherapy drugs have described the nausea and vomiting associated with cisplatin as severe and common (Calvert & McElwain, 1988; Cohen, 1982; Chabner & Myers, 1989). Dacarbazine (DTIC) is believed to frequently cause severe nausea and/or vomiting. The nausea and vomiting associated with DTIC has previously been described as frequent, common, and marked (Calvert & McElwain, 1988; Cohen, 1982; Chabner & Myers, 1989). Adriamycin is perceived to frequently cause moderate nausea and/or vomiting - a view supported by other literature (Calvert & McElwain, 1988; Cohen, 1982; Chabner & Myers, 1989). Carboplatin and Cyclophosphamide are perceived to cause moderate nausea and/or vomiting on about half of the occasions in which they are administered. This view of the emetogenicity of carboplatin is supported by Calvert and McElwain (1988) but is described as mild by Chabner and Myers (1989). Etoposide is perceived to be causing mild nausea and/or vomiting about half the time; a perception supported by other literature (Calvert & McElwain, 1988; Cohen, 1982; Chabner &

Myers, 1989). Vinblastine, 5-FU, Procarbazine, Chlorambucil, Bleomycin, Vincristine, and Levamisole are all perceived to rarely cause mild nausea and/or vomiting. These perceptions are supported by other literature in the case of vinblastine, 5-FU, chlorambucil, bleomycin, and vincristine (Calvert & McElwain, 1988; Cohen, 1982; Chabner & Myers, 1989) but procarbazine is said to cause nausea and/or vomiting more often than this by Calvert and McElwain (1988) and Cohen (1982). Levamisole is not reported in any of the literature mentioned. Prednisone is believed to never induce any nausea and/or vomiting, but this drug also gets no mention in any of the literature.

In order to estimate the emetogenicity of the drug combinations used on the patients in this study, two estimates were derived from the toxicity questionnaire results: one is calculated using the most emetogenic drug in the protocol and the other is calculated using the average emetogenicity of all of the drugs in the protocol. Table 2 shows the two expected emetogenicity estimates for each of the protocols used in this study. When the most emetogenic drug in the protocol is used to determine the emetogenicity of the entire protocol, BEP is the most emetogenic protocol; followed by ABVD; then CHOP , Adriamycin (single agent), and CAP; Carboplatin (single agent); Cyclophosphamide (single agent), CMF, and CHOP (without adriamycin); ChlVPP; and the least emetogenic protocol is 5-FU plus levamisole. When the emetogenicity of a protocol is estimated using the average of the emetogenicity ratings of all of the drugs in a protocol, adriamycin (single agent) is the most emetogenic, followed in order by carboplatin (single agent), ABVD, BEP, Cyclophosphamide (single agent), CAP, CHOP, CHOP with methotrexate IT, CMF, CHOP without adriamycin, ChlVPP, and the least emetogenic protocol is 5-FU plus levamisole.

Table 1.
Individual Drug Emetogenicity

	Toxicity Questionnaire Ratings		
	Frequency	**Severity**	**Emetogenicity**
Cisplatin	3.7	2.9	Always, Severe
Dacarbazine (DTIC)	3.3	2.5	Frequently, Severe
Adriamycin	3	2.4	Frequently, Moderate
Carboplatin	2.3	1.7	Half of the time, Moderate
Cyclophosphamide	2	1.5	Half of the time, Moderate
Etoposide	1.6	1.3	Half of the time, Mild
Vinblastine	1.2	1.2	Rarely, Mild
5-Flourouracil	1	1.1	Rarely, Mild
Procarbazine	1	0.7	Rarely, Mild
Chlorambucil	0.9	0.9	Rarely, Mild
Methotrexate	0.9	0.9	Rarely, Mild
Bleomycin	0.9	0.8	Rarely, Mild
Vincristine	0.8	0.8	Rarely, Mild
Levamisole	0.5	0.5	Rarely, Mild
Prednisone	0.3	0.2	Never

Table 2.
Expected Emetogenicity of the Protocols Used in this Study

	Most Emetic Substance		*Average Emetogenicity*	
	Frequency	**Severity**	**Frequency**	**Severity**
CHOP	3	2.4	1.525	1.225
CHOP+Methotrexate IT	3	2.4	1.4	1.16
Adriamycin	3	2.4	3	2.4
CMF	2	1.5	1.3	1.17
CAP	3	2.4	1.77	1.37
ABVD	3.3	2.5	2.1	1.725
BEP	3.7	2.9	2.07	1.67
Cyclophosphamide	2	1.5	2	1.5
5-FU+Levamisole	1	1.1	0.75	0.8
CHOP without Adriamycin	2	1.5	1.175	0.95
Carboplatin	2.3	1.7	2.3	1.7
ChlVPP	1.2	1.2	0.85	0.75

END POINTS: RESPONSE, REMISSION & CURE

It is important to consider whether the benefits of treatment outweigh the disadvantages. Definite treatment end points or goals must be specified, such as cure or symptom palliation, and treatment effectiveness must be balanced against side effects.

Cure means that the expectation or probability of survival is the same as it would have been had the cancer not occurred.

Complete remission means that all evidence of cancer in the body has disappeared after treatment. This does not always mean cure as a tumour has to have over one million cells before it is detectable. Therefore, chemotherapy should be continued after all detectable tumour has disappeared, to destroy the remaining cells. Complete remission is essential for cure.

Partial remission means that the tumour has decreased by more than half of its original size, which often improves the patient's quality of life and sometimes prolongs it. The cancer usually grows again or relapses at a later date.

QUALITY OR QUANTITY?

Sometimes the side effects of chemotherapy are so severe and distressing that the patient needs to have their dosage reduced or may want to stop the treatment entirely. Aggressive chemotherapy regimens may produce side effects which lead some patients to think that the treatment is worse than the disease. This loss of treatment often means that the patient's life expectancy is shortened considerably. The choice of whether to endure the side effects is entirely up to the patient and often comes down to a decision about whether to have quality of life, with no chemotherapy, or quantity of life, with chemotherapy.

Most patients are undoubtedly prepared to tolerate great discomfort in order to achieve a remission or cure (Slevin et al., 1989), but where no significant survival advantage can be observed between treatments, other aspects of the treatment become important to consider, such as the effects on quality of life. One of the main issues in cancer treatment currently, is the cost at which cancer treatment is achieved in terms of its effects on quality of life.

THE GROWTH OF PSYCHOSOCIAL ONCOLOGY

Concern for the psychological well-being of cancer patients is not new, but psychosocial oncology as a subspeciality of oncology is a recent arrival in the health arena. It has primarily grown from research aimed at understanding and alleviating the emotional and social impact of cancer and its treatment. Essentially, clinical practice in

psychosocial oncology covers the detection of psychological, psychiatric, and social morbidity, the diagnosis of this morbidity, and the provision of treatments designed to alleviate it (Watson, 1992). It is a multidisciplinary area and the skills may be practised by nurses, oncologists, psychologists, psychiatrists, social workers, and a wide range of other professional groups.

SUMMARY

Cancer chemotherapy has been in use for over fifty years and is now used as the definitive treatment for a number of previously untreatable diseases and as an adjuvant treatment for many other diseases. Its main advantage is its ability to treat metastases and its main disadvantage is its toxicity to normal cells in the body. Presently, chemotherapy has the ability to cure some cancers and provide remission to many others, but many still remain resistant to the currently available drugs. Most of the side effects of chemotherapy are controlled by adjusting the drug dosage and by providing support services to the patients when required. When considering the use of chemotherapy it is important to specify the treatment goals and to make sure that the extra duration of life gained from chemotherapy outweighs the physiological and psychological consequences of the treatment. Of special interest to this study is the nausea and vomiting associated with some chemotherapy drugs.

Chemotherapy-Induced Nausea and Vomiting

Nausea and vomiting are the most distressing of all the side effects of chemotherapy (Boakes et al., 1993). The prevalence of posttreatment nausea and vomiting in cancer chemotherapy has decreased over the past fifteen years. A 1980 study by Martin-Jimenez reported that 79% of the patients experienced some degree of vomiting after their first cycle of chemotherapy. Leventhal et al. (1986) reported that 86% of their sample of breast cancer patients experienced some degree of nausea and 47% experienced vomiting to some degree during their treatment. Lindley et al. (1989) reported that 50% of their outpatient chemotherapy patients experienced posttreatment nausea and 27% experienced posttreatment vomiting. It has been reported that over 90% of patients receiving high dose cisplatin experience some degree of nausea and/or vomiting, and that this often occurs more than 24 hours, and lasting up to 120 hours, after the chemotherapy has been administered (Lindley & Hirsch, 1992).

ETIOLOGY

The nausea and vomiting associated with cancer chemotherapy are caused by many different pathologies and in view of this multitude of aetiologies, it seems unlikely that they are governed by a common mechanism. There do, however, appear to be three general components which hold true. Firstly, afferent pathways relay the emetic signal to the central nervous system. Secondly, there is a central reception, recognition and processing area or areas which integrates the emetic signal. Thirdly, the efferent pathways coordinate the respiratory, gastrointestinal and abdominal movements which accompany nausea and emesis.

AFFERENT PATHWAYS

1) Gastrointestinal Tract

Stimulation of vagus nerve branches supplying the stomach elicits vomiting in animal experiments. Chemical irritation of the gastric mucosa by nitrogen mustard or copper sulphate also produces vomiting. Cutting the gastric branches of the vagus nerve abolishes this vomiting response. In vomiting resulting from intestinal obstruction,

biliary colic and cardiac pain, the stimulus appears to be transmitted via sympathetic pathways.

2) Chemoreceptor Trigger Zone (CTZ)

Borison and Wang (1953) identified an area separate from the vomiting centre, situated in the floor of the fourth ventricle within the area postrema. It is not part of the brain and has direct contact with both the cerebrospinal fluid and with circulating blood, thus existing outside the blood-brain barrier. Very little is known about the chemoreceptor trigger zone. This area is known to be sensitive to apomorphine; and ablation of the area in dogs abolishes the vomiting response to apomorphine while the intragastric response to copper sulphate remains intact. The area responds to a very wide range of chemical substances. Over seventeen probable neurotransmitters have been identified in or near the CTZ and hence the mechanisms involved are likely to be extremely complex.

3) Labyrinth

Motion sickness and the vomiting associated with labyrinthitis are mediated via impulses from the labyrinth along the vestibular nerve to the lateral medulla (Reason & Brand, 1975).

4) Other Afferents

Electrical stimulation of the hypothalamus in the cat sometimes induces vomiting and this vomiting may be delayed. Higher centres also have input to the vomiting centre.

VOMITING CENTRE

Borison and Wang (1949) and Borison (1959) were the first to identify the importance of certain sites of the dorsolateral reticular formation of the medulla. Since its function is that of coordinating the multiple physiological reactions in vomiting it may actually be a number of adjacent, closely inter-related sites rather than a single zone. This theory is supported by some electrical stimulation experiments by Miller and Wilson (1983) which failed to localise a single vomiting centre.

There are at least three major inputs into the vomiting centre. Firstly, there is input from the vestibular system, and this is thought to be involved in the development and

expression of nausea and vomiting due to motion (Reason & Brand, 1975). Secondly, input comes from the area postrema, which is thought to be influenced by chemical challenges such as food poisoning and chemotherapy. The third input is from cortical areas from the limbic system and the cerebrum. There are fibre tracts from areas in the limbic system associated with the expression of emotion and associated with memory that connect to the vomiting centre. This provides the neurologic substrate which makes possible the involvement of psychological phenomenon in the expression of nausea and vomiting (Morrow & Dobkin, 1988). Thus, nausea and vomiting may be elicited by diverse circumstances such as the sight of blood or other injury, the sight of another person vomiting, or even the thought of a food or situation that has previously been associated with nausea or vomiting (Andrykowski, 1990).

EFFERENT PATHWAYS

This involves the transmission of signals from the lateral medulla via somatic efferent pathways controlling respiratory and abdominal muscles and visceral efferent components, modifying gastric tone and motility, and also autonomic efferents producing salivation, pallor and sweating.

DIFFERING EMETIC PROBLEMS

There are three types of nausea and vomiting which may occur as a result of chemotherapy: 1) acute chemotherapy induced emesis, 2) delayed emesis, and 3) anticipatory emesis. Patients may also have nausea and vomiting not directly related to their chemotherapy. This may be caused by other medications or by tumour-related complications such as intestinal obstruction or raised intracranial pressure. There are a large number of important factors to consider when deciding what type of antiemetic cover to provide.

IMPORTANT FACTORS IN PLANNING ANTIEMETIC THERAPY:

1) Patient characteristics

- emesis control during prior chemotherapy
- history of alcohol use

- age

2) Chemotherapy

- emetic potential of chemotherapy drugs
- dosage and schedule
- rate of administration
- time of onset of emesis
- consideration of the effects of combining different drugs

3) Antiemetics

- dosage and schedule
- rate of administration
- combination regimens

Patient Characteristics

Patients who have previously experienced poor emetic control are more likely to experience bad control during subsequent treatment. Gralla and colleagues (1981) found that control of emesis was three times more likely if the patient had no previous chemotherapy. The patient's history of alcohol intake is also of importance, with histories of excessive and/or prolonged alcohol intake (>100g/day, or about 5 mixed drinks) making the occurrence of posttreatment nausea and vomiting less likely (D'Acquisto et al., 1986; Sulivan, Leyden & Bell, 1983). However, this does not imply that alcohol is an antiemetic or that antiemetic therapy is not needed in patients with prior heavy alcohol use. It may indicate that some of the receptor sites involved in nausea and vomiting are less sensitive in patients with such a history. The age of the patient may also influence the choice of antiemetics, as there is an increased incidence of acute dystonic reactions (muscle spasms in the neck, mouth or face due to the effects of phenothiazines) in younger patients given antiemetics that act by blocking dopamine receptors. This makes the use of 5-HT_3 receptor blockers a more attractive option in younger patients.

Chemotherapy Drugs and Emesis

The chemotherapy agents which are most often associated with nausea and vomiting also induce the most severe nausea and vomiting. In patients who have not previously

received chemotherapy, emesis typically begins 1-2 hours after the chemotherapy has started. There are exceptions to this, with high dose cyclophosphamide producing emesis which may be delayed for 9-18 hours after the chemotherapy has begun (Fetting, Grochow, Folstein, et al., 1982). An antiemetic regimen must consider the individual pattern and potential for causing emesis of each chemotherapy drug and when combination chemotherapy is used, the emetic pattern and potential of the drugs in combination must be considered.

Antiemetic Agents

No single antiemetic agent is ideal for the control of chemotherapy induced nausea and vomiting. An appropriate combination can often be more useful than a single drug. A more extensive description of the antiemetic agents available is provided in the section on the pharmacological treatment of nausea and vomiting.

SUMMARY

Posttreatment nausea and vomiting is one of the most frequently reported side effects of chemotherapy. The nausea and vomiting associated with cancer chemotherapy is the result of a complex, and largely unknown, physiological and psychological process. The tolerance level of each patient varies greatly, both between and within individuals. Some can tolerate four or five hours of nausea and vomiting, whereas others would discontinue their treatment under these conditions. Some experience the same level of nausea and vomiting during all of their treatments, while others have an increase or decrease in their level of nausea and vomiting. Also, some may become more tolerant as their treatments progress, while others become less tolerant. The substantial individual differences in ability or willingness to tolerate chemotherapy side effects suggest that psychological factors play a critical role in translating drug side effects into emotional distress, disruption of life activities, and refusal to continue treatment (Nerenz et al., 1984).

Anticipatory Nausea and Vomiting

As if the pharmacological side effects of chemotherapy are not enough, there has been a constant stream of reports in recent years of the frequent development of anticipatory nausea and vomiting (ANV) associated with chemotherapy, where the patient experiences nausea and vomiting before the emetic chemotherapy drugs have been administered (Redd & Andrykowski, 1982). There are, however, definitional problems that have emerged in the literature. These have resulted in a large amount of variance between studies, with many patients who would have been counted as having developed ANV being left out and many who may not have had ANV being labelled as having ANV. This issue is discussed below and a solution is proposed.

ANV is typically conceptualised in terms of a classical conditioning paradigm, where the patient initially responds to the chemotherapy drugs (unconditioned stimuli) with posttreatment nausea and/or vomiting (unconditioned responses). When the chemotherapy is delivered there are usually other things present (conditioned stimuli) that come to be associated with the chemotherapy drugs and the posttreatment nausea and vomiting, and after a number of pairings they may come to elicit anticipatory nausea and/or vomiting (conditioned responses) in the absence of the chemotherapy drugs. The evidence for this theory is discussed below and a number of other theories of aetiology are mentioned.

Much research has been conducted with respect to the factors that are related to the acquisition of this response (Dobkin, Zeichner, & Dickson-Parnell, 1985; Cohen et al., 1986; Andrykowski, Redd & Hatfield, 1985). Many factors have been implicated, with a few appearing in the majority of the literature, and their role in the acquisition of ANV will be discussed in more detail later.

The treatment of ANV using behavioural techniques has been less than adequately pursued or documented, despite evidence which shows that methods such as hypnosis, progressive relaxation training, systematic desensitisation, and a variety of other techniques are very effective in reducing anticipatory nausea and vomiting, posttreatment nausea and vomiting, and the anxiety and depression associated with treatment - generally making the experience a lot less stressful (Morrow & Dobkin,

1988; Burish & Carey, 1986; Redd & Andrykowski, 1982). The use of behavioural treatments is discussed later, and their mode of action is considered.

DEFINITION & ASSESSMENT

Most research has been less than rigorous with respect to defining exactly what ANV is (Andrykowski, 1986). Some researchers have even failed to specify how they defined ANV. When specified, there are three basic classes of definition: nausea and/or vomiting prior to or during the chemotherapy infusion; nausea and/or vomiting prior to the infusion; and either of the above two, with some qualifying statement added, such as 'without another cause for such' or 'associated with some treatment-related stimulus'. There are problems with all three of these definitions, in that they will often pick up episodes of nausea and/or vomiting that are attributable to physiological or pharmacological factors.

The first definition, which includes nausea and/or vomiting prior to or during the infusion, may pick up a lot of 'false positives' due to the posttreatment nausea and vomiting starting while the infusion is still being administered. This is especially problematic if the chemotherapy protocol involves lengthy infusions of two hours or more (Andrykowski, 1986). Both the first definition and the second, which includes nausea and/or vomiting prior to the infusion, may pick up 'false positives' if the chemotherapy protocol includes oral medication taken over a long period of time, as these drugs may be responsible for the nausea and/or vomiting prior to the infusion (Andrykowski, 1986). The third definition, although narrowing the range of responses that can be characterised as ANV, still has the same inherent problems as the other two definitions. Andrykowski (1986) has offered a definition that restricts the definition of ANV to reports of nausea and/or vomiting prior to a treatment on day one of a chemotherapy cycle. This usually ensures that the patient has not received any emetic drugs for at least a week. It therefore greatly reduces the likelihood that the observed nausea and vomiting is the result of physiological or pharmacological factors, producing a more homogeneous criterion group of patients with ANV. Burish and Carey (1986) have suggested a modification of Andrykowski's definition, preferring to use two

operational criteria for identifying ANV: the symptoms should be measured a) before the chemotherapy drugs are infused and b) after the assumption can reasonably be made, based on the pharmacological properties of the drugs, that any previously administered medications have cleared the system. For the purpose of this study, anticipatory nausea and vomiting will be defined as, and restricted to, reports of nausea and/or vomiting in the 48 hours prior to treatment on day one of a chemotherapy cycle.

PREVALENCE

There have been a large number of prevalence rates found with respect to ANV, ranging from 18% (Nicholas, 1982) to 63% (Cella et al., 1984) of patients receiving cancer chemotherapy. The prevalence rates generally range from 20-40% (Bernstein, 1991). This variance is due to at least four factors: definitional problems, variability in treatment protocols, difference in time of assessment, and methodological variance (Burish & Carey, 1986). The definitional problems have already been discussed and the remaining three factors will be discussed below.

Most studies present data from patients receiving extremely varying types of chemotherapy and also different antiemetic agents are commonly presented together. Thus, because ANV is closely related to the presence of posttreatment nausea and/or vomiting, which in turn is affected by the emetogenicity of the chemotherapy and the success or failure of the antiemetic agents, there is considerable variance in the prevalence of ANV across patients on different chemotherapy protocols as well as between patients on the same protocol (Burish & Carey, 1986).

There is also substantial variability between studies in the number of treatments the patient has received prior to being assessed for the presence of ANV. For example, Wilcox et al. (1982) assessed their subjects prior to the tenth chemotherapy cycle whereas Morrow et al. (1982) assessed their subjects prior to the fourth cycle. This may account for much of the variability, due to the relationship that has been established between the number of treatments completed and the development of ANV.

Much of the variance in prevalence is probably the result of methodological variance between studies (Burish & Carey, 1986). A wide variety of measures have been used to

assess nausea and vomiting. For example, several investigators have used a visual analogue scale to assess how nauseated their subjects were (Olafsdottir et al., 1986; Ahles, 1984; Adrykowski, Redd & Hatfield, 1985); others have used self-report questionnaires (Dobkin et al., 1985; Weddington, Miller & Sweet, 1984); while others have used the Morrow Assessment of Nausea and Emesis (MANE) self-report scale to measure the frequency, duration, and peak intensity of anticipatory nausea and vomiting, and posttreatment nausea and vomiting (Morrow, 1984; Cohen et al., 1986). Another measurement inconsistency that has contributed to the variance in prevalence rates is the amount of recall required of patients (Burish & Carey, 1986). This is a problem, as a report by Stunkard et al. (1985) revealed a significant difference between concurrent and retrospective recall, with the retrospective data exaggerating vomiting frequency - suggesting that the use of concurrent reporting will produce more accurate prevalence rates. Overall, there is not yet a widely used and convincingly validated instrument or procedure for measuring nausea and vomiting (Burish & Carey, 1986). It is believed that these four factors, including definitional problems, variability in protocols, difference in the time of assessment, and methodological variability, could account for about 10 of the 40 percent prevalence rate reported (Morrow & Dobkin, 1988).

If all of the studies are taken into account and combined to achieve an estimated prevalence rate for ANV, about 32% of patients receiving chemotherapy report ANV (Burish & Carey, 1986). If only the prospective, longitudinal studies are considered (i.e., Andrykowski et al., 1985; Jacobson et al., 1985; Love et al., 1985), the prevalence rate is about 45%. A more recent study by Boakes et al. (1993) reports that 41% of their patients developed at least 'mild' anticipatory nausea and that 24% developed 'moderate to severe' anticipatory nausea.

CORRELATES & PREDICTORS

Univariate Correlates

There are three groups of variables that have been shown to correlate significantly with the presence of ANV. These are demographic variables, clinical variables and psychological variables.

(1) Demographic Variables- Age is the only demographic variable that has been consistently shown to have any predictive value, with younger (under 50) patients showing an increased incidence of ANV (Morrow & Dobkin, 1988; Burish & Carey, 1986). The reason for this is not known but there are a number of theories, including one that uses evidence from classical conditioning. Novel stimuli are more easily conditioned, and since young people are more likely to be encountering novel stimuli during their treatment, conditioning of ANV in young people is more likely. Another theory is that younger people get more noxious tumours than older people and there is some evidence to support this as well (Redd & Andrykowski, 1982).

Only two studies, out of a possible eleven looking at gender have found a significant correlation, with an increased likelihood of developing ANV in females (Fetting et al., 1983; Wilson et al., 1986). Ethnicity, education level, socioeconomic and marital status have all demonstrated no significant or consistent relationship with ANV (Morrow & Dobkin, 1988; Andrykowski, 1986; Burish & Carey, 1986).

(2) Clinical Variables - The length of treatment, or the number of treatments completed, is significantly and consistently correlated with a higher incidence of ANV; as is more lengthy and intense posttreatment nausea and vomiting (Morrow & Dobkin, 1988). Another clinical variable that has been associated with a higher incidence of ANV is a susceptibility to motion sickness, with those who are susceptible to motion sickness having significantly more side effects from the chemotherapy drugs, significantly more posttreatment nausea and vomiting, and significantly more ANV (Morrow, 1984; 1985; Leventhal et al. 1988).

(3) Psychological Variables - Increased anxiety, both state and trait anxiety, is the most consistent psychological variable which correlates with ANV (Burish & Carey, 1986; Morrow & Dobkin, 1988). Depression, hostility and coping styles have also been studied in chemotherapy patients, with two studies out of a possible four finding a relationship between elevated levels of depression and ANV (Cohen, 1982; van Komen & Redd, 1985), one study out of three finding a relationship between increased hostility and ANV (Ingle et al., 1984), and one study out of three finding a significant relationship between more coping attempts made and ANV (Ingle et al., 1984). It is

possible however, that the variability in the findings from studies on these factors is due to measurement variance rather than actual differences in response (Morrow & Dobkin, 1988).

Multivariate Correlates

Many of the recent studies on ANV point to the role of interactive relationships among the demographic, clinical and psychological variables mentioned above which might be associated with the development of ANV. Morrow (1982) found that he could get an 80% accurate retrospective classification of ANV by using a combination of age, and the severity and duration of posttreatment nausea and vomiting, whereas Ingle et al. (1984) found that they could get a 71% accurate classification by using age, posttreatment nausea and vomiting, anxiety and coping success. Cohen (1982) found that 80% of the variance between subjects could be accounted for by anxiety, noxious sensations (tastes and odours), age, and the frequency of posttreatment nausea and vomiting. It has also been found that 24% of the variance could be accounted for by the level of posttreatment nausea alone, and that a significant portion of the remaining variance could be accounted for by state anxiety (anxiety in response to the treatment), and the length of time it takes to administer the drugs (Andrykowski, Redd & Hatfield, 1985).

Morrow (1984) stated that patients with ANV were significantly more likely to have four or more of the following features:

a) Less than 50 years of age.

b) Nausea and/or vomiting after their last treatment.

c) Described their nausea after the last treatment as 'moderate, severe, or intolerable'.

d) Described their vomiting after the last treatment as 'moderate, severe, or intolerable'.

e) Report the side effect, 'warm or hot all over', after the last treatment.

f) Susceptible to motion sickness.

g) Experienced 'sweating' after the last treatment.

h) Experienced 'generalised weakness' after the last treatment.

To summarise this section, the variables that have been found to correlate with ANV in many studies are: high levels of posttreatment nausea and/or vomiting; age (younger); higher doses, greater amounts or more emetogenic drugs; and higher levels of anxiety or general distress (especially state anxiety). The variables that have been found to correlate with ANV in only one study or by only one group of investigators are: more coping strategies tried (Ingle et al., 1984); inhibitive rather than facilitative coping style (Altmaier, Ross & Moore, 1982); prior history of motion sickness; parents with high anxiety levels (paediatric patients only); long infusions rather than short (Andrykowski, Redd & Hatfield, 1985); large group treatment room rather than a private room (van Komen & Redd, 1985); itching, taste and smell sensations during treatment (Nicholas, 1982; Nerenz, Leventhal & Love, 1982 respectively); and being unmarried (Fetting et al., 1983).

ETIOLOGY

There have been seven different models of aetiology proposed for the development of ANV in chemotherapy patients: physiological, autonomic reactivity, psychodynamic, coping, anxiety, taste aversion, and learning models. Below is a brief discussion of these models, with most of the attention focused on the learning model, as this seems to be the most widely accepted model of aetiology (Morrow & Dobkin, 1988; Bernstein, 1991; Burish & Carey, 1986).

Physiological Model

The physiological view is that anticipatory symptoms may be produced by brain metastasis or local cancer involvement of the gastrointestinal tract (Chang, 1981). This model is opposed by at least two findings: the first is that the metastatic spread of cancer to the brain or gastrointestinal tract is much less prevalent than ANV; and secondly, there seems to be no association between metastatic disease and ANV (Morrow & Dobkin, 1988).

Autonomic Reactivity Model

This model proposes that increased autonomic reactivity is an accurate individual marker for ANV susceptibility (Kvale et al., 1991). There is evidence to support this, in

that patients who have been shown to have high levels of autonomic reactivity, as measured by heart rate and peripheral vascular changes in response to auditory stimuli, have been more likely to develop ANV (ibid., 1991). This model is closely related to the learned model, in that it is based on the relationship between reactivity and the conditioning process. It has been shown that spontaneously high reactive individuals show conditioned responses to phobic scenes more easily (Hugdahl, Fredrikson, & Ohman, 1977), and also that autonomic reactivity is predictive of both acquisition and extinction of conditioned responses (Ohman & Bohlin, 1973).

Psychodynamic Model

According to this view, nausea and vomiting 'are not always direct side effects of chemotherapy, but rather may be surfacing manifestations of underlying psychological readjustment problems associated with life-threatening illness' (Chang, 1981). This model suggests that these side effects may be caused by psychological mechanisms, including anger, anxiety, and frustration. There is no direct empirical support for this model, although increased levels of anxiety have been measured in patients with ANV (Morrow & Dobkin, 1988; Redd, Burish & Andrykowski, 1985).

Coping Model

This model suggests that patients who develop ANV may be deficient in their ability to adjust to, or cope with, the physical and emotional challenges associated with their chemotherapy treatments. The increased levels of anxiety shown in patients with ANV may be seen as a failure to cope effectively (Morrow & Dobkin, 1988). It has been reported that patients with ANV demonstrate significantly less desire and ability to cope than patients without ANV (Altmaier et al., 1982), although these researchers' method of assessing coping has never been validated or replicated. Ingle et al. (1984) found a positive correlation between the number of ways the patient had tried to cope with having cancer and the development of ANV - in that their initial coping strategies may have been inadequate or deficient. However, the methodology of this study was also questionable, using retrospective self-report measures of nausea and vomiting, so these findings must be treated with caution.

An alternative coping model recognises a three-way interaction between physical and psychological demands of the medical situation and the coping resources of the individual (Gil, 1984). This theory identifies three channels of responses: overt behavioural, physiological, and cognitive. So, any difference in physical, psychological or coping ability will lead to a different response to the chemotherapy situation. The physical and psychological factors might include the administration of toxic chemicals, symptoms of the disease, concern about prognosis, fear of injections, etc; and the coping resources may include overt behavioural control, cognitive control, or physiological control (Morrow & Dobkin, 1988).

Anxiety Model

Houts et al. (1984) have proposed four potential ways that anxiety might relate to ANV: 1) anticipatory nausea may cause pretreatment anxiety; 2) pretreatment anxiety may cause anticipatory nausea; 3) anticipatory nausea and pretreatment anxiety may both be caused by posttreatment nausea; or 4) pretreatment anxiety may facilitate the conditioning process of ANV. There is some data to support all of these potential explanations so it is unclear if any of them are correct, or maybe there are a variety of different ways in which anxiety interacts with ANV in different people (Morrow & Dobkin, 1988).

Andrykowski et al. (1985) showed that elevated levels of state anxiety may precede the initial occurrence of ANV, although they stress that the relationship between anxiety and ANV may not be a strictly causal one. Their data does support the view that heightened anxiety following a treatment may increase posttreatment nausea and/or vomiting, which in turn may increase the susceptibility to conditioning on the next treatment - facilitating and promoting a conditioning process rather than serving as a direct cause. This would support the explanation that anxiety is involved in some form in the conditioning of side effects (Morrow & Dobkin, 1988).

Taste Aversion Model

In the taste aversion model animals use the taste and smell of particular substances as cues for avoiding substances that have made them ill in the past and there is evidence that these tastes and smells have become aversive or noxious. This learning may occur

very rapidly; often requiring only a single episode. Bernstein and Webster (1980) demonstrated that human subjects could acquire learned taste aversions in a single trial when consumption of food (a novel-favoured icecream) was followed by nausea and vomiting induced by chemotherapy. Taste aversion experiments have revealed that the mammalian learning mechanisms do not operate randomly, associating stimuli and reinforcers only as a function of recency, frequency and intensity. Mammals associate gustatory and olfactory cues with internal malaise even when these stimuli are separated by long time periods (Garcia, Ervin & Koelling, 1966).

Lorenz et al. (1986) and Fetting et al. (1983) reported that patients who noticed a taste of drugs during chemotherapy injection were more likely to develop anticipatory nausea and vomiting than patients who did not notice a taste. However, more recent studies have been unable to replicate this finding (Andrykowski, 1987; Morrow, 1989).

Learned Model

This model states that ANV is acquired through a classical conditioning process in which environmental cues become associated with drug delivery and later act to trigger responses similar to those which are elicited by the drugs (Bernstein, 1991). An operant learning model does not seem to be appropriate for the development of ANV, as this model would state that the patient receives some form of reward and/or avoids or escapes from some noxious consequence. Although the patient may receive increased attention from their nurses, doctors, friends and family, it is difficult to imagine how this would be reinforcing enough to encourage further nausea and vomiting (Morrow & Dobkin, 1988).

According to the classical conditioning model the probability of developing ANV increases with the number of chemotherapy treatments and with the severity of posttreatment symptoms of nausea and vomiting. Posttreatment nausea and/or vomiting are necessary for the development of ANV under this model; a fact which is supported by most research (Redd & Andrykowski, 1982). In the classical conditioning model, the intensity and novelty of the conditionable stimulus influence the ease with which that conditionable stimulus may become conditioned. Therefore, a more intense and/or novel stimulus has the potential to become a stronger conditioned stimulus with fewer pairings

needed to establish the conditioning. Also of interest in classical conditioning is the concept of biological preparedness, where it may only take one pairing of a certain type of food with the sickness reflex to condition a strong negative response to that food in the future. This phenomenon has lead to the study of taste aversion as a subtype of classical conditioning.

A classical conditioning explanation of how ANV might develop is outlined in Figure 1 below (Morrow & Dobkin, 1988). An unconditioned response (posttreatment nausea and/or vomiting) which follows an unconditioned stimulus (the chemotherapy drugs administered) in the context of potentially conditionable stimuli (sensations, thoughts, images of the clinic and/or nurse, etc) will, after a number of repeated trials (chemotherapy treatments), give rise to a conditioned stimulus (such as the chemotherapy nurse) eliciting a conditioned response (anticipatory nausea and vomiting).

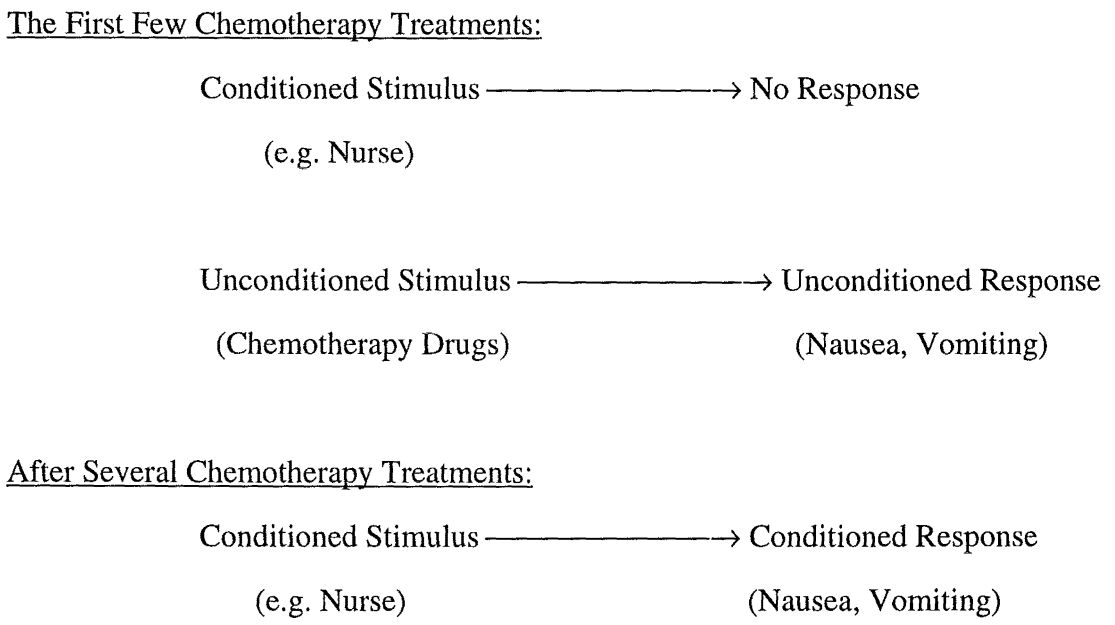

Figure 1. *Classical Condition Model for the Acquisition of ANV.*

Support for this view comes from many different observations that conform to the classical conditioning paradigm, including the course of development, stimulus generalisation, correspondence between unconditioned and conditioned responses, the

intensity of the unconditioned response, and higher order conditioning (Morrow & Dobkin, 1988).

Course of Development: ANV develops only after a number of administrations of chemotherapy drugs have been given (Morrow et al., 1982). In fact, ANV is virtually never seen before a number of administrations have been given. The percentage of patients with ANV increases with the number of treatments given (Morrow, 1982; Olafsdottir, Sjoden & Westling, 1986). This observation is consistent with the development of a learned response where the strength of that response (ANV) increases with the number of conditioning trials (treatments).

Stimulus Generalisation: The learning phenomenon of stimulus generalisation, where there is a response to a stimulus similar to the original conditioned stimulus, fits the available clinical data on ANV. It has been observed that the patients ANV may be elicited by an increasing range of stimuli and situations as the treatment progresses (Redd & Andrykowski, 1982). Nausea may even be induced by mental images of the chemotherapy setting (Redd et al., 1993).

Correspondence Between Unconditioned and Conditioned Responses: Many studies have shown that there is a relationship between the occurrence of posttreatment nausea and/or vomiting and the likelihood of an individual developing ANV (Morrow & Dobkin, 1988). There has been no reported case of ANV without some degree of posttreatment nausea and/or vomiting. Also, the anticipatory nausea and vomiting (CR) closely resembles the posttreatment nausea and vomiting (UCR), fitting in with the classical conditioning model.

Intensity of Unconditioned Response: The intensity of the posttreatment nausea and vomiting affects the development of ANV, with greater posttreatment nausea and vomiting leading to a higher incidence of ANV (Morrow & Dobkin, 1988).

Higher-Order Conditioning: Through higher-order conditioning, neutral stimuli can come to elicit a conditioned response by being paired with a prior conditioned stimulus, rather than an unconditioned stimulus as in first-order conditioning. Generally, a higher-order conditioned stimulus does not elicit a conditioned response as strong as a first-order conditioned stimulus. This all fits in quite well with ANV, as the patient will often

get increasing ANV as he/she gets closer to the treatment setting, the first-order conditioned stimulus (Olafsdottir et al., 1986; Nicholas, 1982).

Critique of the Learning Model

There are at least two characteristics of ANV that do not fit comfortably within the learning model outlined above. Firstly, in conventional classical conditioning the UCS-UCR interval is typically only a few seconds or possibly minutes and the shorter the interval, the better the conditioning. When we look at the UCS-UCR interval in chemotherapy treatment, the time between receiving the drugs and experiencing the posttreatment nausea and/or vomiting, is usually measured in hours rather than seconds or minutes. However, this may not be a problem if we look at the evidence from taste-aversion experiments which shows that conditioning involving the gastrointestinal system (as nausea and vomiting do) can occur with intervals up to 8 or 9 hours (Robertson & Garcia, 1985). The learned taste-aversion model would further predict that the patient does not have to be aware of the nausea (UCR) for conditioning to occur; so in cases where the patient is medicated below the threshold of conscious awareness, ANV could still develop (Morrow & Dobkin, 1988). Whether this is true has yet to be proven.

Secondly, the conditioned response in classical conditioning usually occurs following each presentation of the conditioned stimulus, but the conditioned response of ANV is often not present prior to every treatment after ANV has initially been conditioned (Morrow & Dobkin, 1988). One explanation for this may be that the conditioned stimulus is not present prior to each chemotherapy treatment. For example, if the treatment room has become part of the conditioned stimulus, the patient may not be treated in the same room during each treatment. There is no data to support or reject this hypothesis as yet.

SUMMARY

Anticipatory nausea and vomiting is a phenomenon which has received much attention recently. For this study ANV is defined as, and restricted to, reports of nausea and/or vomiting in the 48 hours prior to treatment on day one of a chemotherapy cycle.

A wide range of prevalence rates have been reported, from 18% (Nicholas, 1982) up to 63% (Cella et al., 1984); with the prevalence rates generally ranging from 20-40% (Bernstein, 1991). Age is the only demographic variable that has been consistently shown to have any prediction value, with younger (under 50) patients showing an increased incidence of ANV. The length of treatment, or the number of treatments completed, more lengthy and intense posttreatment nausea and vomiting, and susceptibility to motion sickness have all been shown to have a significant correlation with ANV. Increased anxiety in those who develop ANV, both state and trait anxiety, is the most consistent psychological variable which correlates with ANV. Depression, hostility and coping styles have also been studied in chemotherapy patients with no consistent relationship shown between these variables and ANV. Many models of acquisition have been proposed, with the classical conditioning model receiving the most support, although there is also some support for the taste aversion model and the anxiety model of aetiology - perhaps indicating that the acquisition of ANV does not follow one specific model but can develop as a result of several different processes.

Management of Posttreatment and Pretreatment Nausea and Vomiting

There are seven different types of treatment that have been used for ANV: pharmacological agents and six behavioural treatments - including progressive muscle relaxation, hypnosis, systematic desensitisation, EMG biofeedback, stimulus control, and stress inoculation training.

PHARMACOLOGICAL TREATMENT

Over half of the patients who undergo cancer chemotherapy experience significant posttreatment nausea and vomiting (Redd et al., 1993). It has been widely accepted that the use of traditional antiemetic drugs (i.e. phenothiazines) for nausea and vomiting associated with chemotherapy is not effective for a large proportion of patients, so it is not surprising that traditional pharmacological treatments do little to alleviate ANV (Redd & Andrykowski, 1982). As well as being ineffective, many are disliked due to their severe sedative effects and the fact that many of them cause muscle tremors, rigidity or fatigue (particularly in the young and elderly). There are, however, new methods for the use of antiemetic drugs which involve the use of multiple agents well before the treatment begins rather than the traditional method of administering the drugs just prior to, or even after, the emetic agents have been given (Andrykowski & Redd, 1987). There is also a new class of antiemetic available, the 5-HT_3 receptor antagonists, which have demonstrated greater antiemetic efficacy against chemotherapy induced nausea and vomiting than the other antiemetics available today. If an effective pharmacological treatment could be found then it could theoretically prevent, or at least postpone the development of ANV, as a weaker unconditioned response (nausea and vomiting) would lead to weaker conditioning or delayed conditioning.

5-HT_3 Receptor Antagonists

The development of highly selective and specific antagonists of neuronally located 5-HT receptors allowed a detailed characterisation of the recognition site which was classified as the 5-HT_3 receptor (Bradely et al., 1986). The possibility that 5-HT_3 receptor antagonists might control chemotherapy-induced nausea and vomiting came

with the realisation that intravenous administration of high doses of metoclopramide provided the most effective antiemetic treatment (Gralla, 1983), and it is known that metoclopramide inhibits the effects of 5-HT (Fozard & Mwaluko, 1976).

Ondansetron (Zofran) is the most extensively investigated 5-HT_3 receptor antagonist and is currently in clinical use around the world, including the oncology department where this study was conducted. Another 5-HT_3 receptor antagonist, granisetron (Kytril), was also available for use during this study. Ondansetron and granisetron have comparable efficacy, and are each reported to provide complete control in 65-70% of those patients receiving cisplatin-containing regimens and complete control in around 86% of those receiving non-cisplatin regimens (Bleiberg, 1992; Plosker & Goa, 1991). The side effects of ondansetron are headaches and constipation in less than 15% of patients and an insignificant liver enzyme increase on rare occasions (Bleiberg, 1992). The side effects of granisetron are headaches in 10-15% of patients, constipation, diarrhoea and somnolence on rare occasions, and transient changes in blood pressure (Plosker & Goa, 1991).

Ondansetron was used primarily in oral form, with 8mg being taken just before receiving the chemotherapy drugs and again eight and sixteen hours after the first administration. This dose of ondansetron has an active period of around eight hours, so the three doses provided cover for the twenty-four hours after the chemotherapy. Granisetron was given intravenously in a 3mg dose just before receiving the chemotherapy drugs. The single 3mg dose of granisetron also provided twenty-four hours of antiemetic cover, with granisetron being the antiemetic used in cases where the chemotherapy regimen involved infusions over a few days, such as the BEP treatment for testis cancer.

Substituted Benzamides

Metoclopramide is the most popular drug of this class. Metoclopramide increases lower oesophageal pressure and enhances gastric emptying, although other central effects contribute to its antiemetic activity. Standard doses of metoclopramide (10-20 mg) are not as effective as high dose metoclopramide (1-2 mg/kg or approximately 100mg) in the treatment of chemotherapy induced nausea and vomiting. High dose

metoclopramide has been shown to be superior, or at least equivalent, to all other antiemetic agents, except 5-HT_3 antagonists, against cisplatin-induced emesis and has demonstrated good antiemetic activity against the emesis associated with a wide range of chemotherapeutic agents (Gralla, 1982). High doses of metoclopramide have been found to be highly effective, with about half of those studied achieving complete emetic control and about two thirds having a 'major response' to the drug (Garnick, 1983; Anthony et al., 1986). The side effects associated with metoclopramide are: mild sedation, akathisia (restlessness), acute dystonic reactions (age-related), and diarrhoea. The dystonic reactions may be controlled by diphenhydramine or lorazepam (Cadman, 1977). Dexamethasone increases the efficacy of metoclopramide and reduces the diarrhoea associated with it. Metoclopramide (Maxolon) was used in standard doses of 10-20mg, both intravenously and orally, in this study.

Phenothiazines

Prior to the introduction of high dose metoclopramide, phenothiazines were the most commonly used antiemetics in chemotherapy patients. They work by disrupting dopamine transmission in the chemoreceptor trigger zone. Phenothiazines do not work well with the more emetic chemotherapy agents; being less active than high dose metoclopramide (Gralla et al., 1981) and dexamethasone (Markman et al., 1984), and equivalent to or less active than THC (Frytak et al., 1979). The side effects of the phenothiazines include orthostatic blood pressure changes, extrapyramidal effects (restlessness), and sedation. The extrapyramidal effects can be prevented or controlled with diphenhydramine.

Butyrophenones

Haloperidol (oral) and Droperidol (intravenous) are the more commonly used drugs in this class. They also work by interrupting dopamine transmission in the chemoreceptor trigger zone. There is no substantial difference in efficacy between haloperidol and droperidol, so haloperidol is used more often due to its more convenient route of administration. The butyrophenones are not as effective as metoclopramide in the prevention of chemotherapy induced nausea and vomiting (Grunberg et al., 1984).

The side effects associated with the butyrophenones are sedation, dystonic reactions, akathisia, and occasionally hypotension.

Cannabinoids

Sallan and colleagues (1975) were the first to publish reports from patients who described less nausea and vomiting from their chemotherapy while being 'high' after smoking marijuana. Consequently it was discovered that the active agent in marijuana, delta-9-tetrahyrocannabinol (THC), possessed antiemetic properties. Two types of cannabinoids are available for clinical use; THC, and a synthetic cannabinoid. Cannabinoids have been found to be equivalent or superior to oral prochlorperazine (Frytak et al., 1979). However, there are many side effects associated with the cannabinoids; including sedation, dizziness, dry mouth, euphoria, dysphoria, paranoid ideation, orthostatic hypotension, and ataxia. Metoclopramide and dexamethasone are more effective and have far fewer side effects (Mitchell, 1992).

Corticosteroids

Many studies have confirmed the utility of corticosteroids as antiemetics although the mechanism of action of the corticosteroids remains unknown (Gralla, 1982). Dexamethasone and methylprednisone are the best studied agents in this class, with dexamethasone being the more popular of the two. They have been found to be especially useful when combined with other antiemetic agents (Rosel et al., 1985). The side effects associated with these drugs are minimal with short-term use, but with long-term use there may be mood changes and a potential for gastric ulceration. Dexamethasone was used in doses of 8-16mg, intravenously and orally, in this study.

Benzodiazapines

These drugs make useful additions to antiemetic regimens rather than acting on their own (Gralla, 1982). Lorazepam is the most studied drug in this class. The major side effect of this drug is sedation.

Summary of Available Antiemetics

Until the early 1980s it was widely believed among medical practitioners that chemotherapy induced nausea and vomiting were a minor problem of cytotoxic treatment (Martin, 1992). The introduction of the highly emetogenic chemotherapy drug

cisplatin was the main force behind the search for more effective antiemetics. The first major step was the introduction of high-dose metoclopramide, which was shown to provide complete emetic control for the twenty-four hours following chemotherapy infusion in approximately one-third of patients treated with cisplatin-based regimens (Gralla et al., 1981). High-dose metoclopramide became the cornerstone of antiemetic treatment in cisplatin-treated patients during the 1980s and also demonstrated its superiority over other antiemetics with patients receiving non-cisplatin regimens (Tyson et al., 1982; Allan et al., 1986). In the early 1990s the 5-HT_3 antagonists ondansetron and granisetron became available, and proved to be more efficacious and less toxic than high-dose metoclopramide with both cisplatin-based and non-cisplatin regimens (Marty et al., 1990; Bonneterre et al., 1990). It is now possible to provide complete emetic control for approximately 65-85% of all patients receiving chemotherapy (Bleiberg, 1992).

PSYCHOLOGICAL TREATMENTS

Progressive Relaxation Training (PRT)

Progressive muscle relaxation training is a commonly used behavioural technique which involves learning how to relax by actively tensing and relaxing various muscle groups in a progressive manner (Masters et al., 1987). The procedure typically involves being taught by a therapist, where a training tape is made, and the individual is told to practice at home using the training tape in order to acquire the ability to relax whenever it is necessary. PRT has been used by cancer chemotherapy patients to reduce side effects, such as posttreatment nausea and vomiting, depression, and anxiety; but its effect on ANV has yet to be investigated.

Lyles et al. (1982) found that relaxation training, with guided imagery, resulted in less nausea and vomiting both during and after the patient's chemotherapy infusion, less anxiety, less physiological arousal, and less depression following the treatment. Burish et al. (1987) investigated whether PRT could be used to prevent or at least lessen chemotherapy side effects through early intervention. The patients who received PRT reported less nausea during and following chemotherapy, as well as less vomiting, lower

physiological arousal, less depression, and a progressive reduction in posttreatment nausea and vomiting over time - with only 10% of the PRT patients experiencing posttreatment nausea compared to 54% of the control patients. Relaxation training does appear to provide symptom relief to chemotherapy patients during and after the administration of the drugs (Morrow & Dobkin, 1988).

Hypnosis

Hypnosis could be described as a state of intensified attention and receptiveness, and an increased responsiveness to an idea or set of ideas (Erickson, 1959). Most of the studies that have used hypnosis to treat ANV have been carried out with paediatric patients as children are more readily hypnotised than adults (Morrow & Dobkin, 1988). Three controlled studies have examined the use of hypnotherapy with patients experiencing ANV. Redd and colleagues (1982) individually instructed each patient in focusing attention, achieving deep muscle relaxation, and imagining pleasant scenes. Most of the subjects, who were all females, showed a decrease in posttreatment nausea and vomiting, and elimination of ANV. Cotanch et al. (1985) trained children who were experiencing particularly troublesome nausea and vomiting in self-hypnosis, involving a combination of relaxation training and hypnosis. Consequently, there was a significant reduction in nausea and vomiting, and a significant increase in oral intake of food. Zeltzer, LeBaron and Zeltzer (1988) compared hypnotherapy to supportive counselling and found that both groups of children reported reductions in nausea and vomiting, and rated chemotherapy as less noxious following intervention with no significant difference in outcome between the two groups. It has been suggested that nonspecific therapy effects, such as demand characteristics and/or extra attention given, may contribute to the effects of treatment (Morrow & Dobkin, 1988). It may also be argued that it is the induction of relaxation which provides the therapeutic results observed with the use of hypnosis, although there has been no study which has used hypnosis without a relaxation component.

Systematic Desensitisation (SD)

Systematic desensitisation is a widely used behaviour therapy treatment for anxieties, fears and phobias. It involves the substitution of one response, generally muscle

relaxation, for the unwanted behaviour. During the systematic desensitisation treatment that has been used in cancer patients, patients imagine scenes from a hierarchy of events related to chemotherapy treatment while remaining deeply relaxed. In this way, treatment stimuli become associated with relaxation so that when the patient encounters stimuli, such as the treatment room, they respond with relaxation rather than ANV (Morrow & Dobkin, 1988).

Morrow and Morrell (1982) found that SD produced a significant reduction in the frequency, severity, and duration of ANV. Morrow (1986) found that SD was significantly better than counselling, relaxation alone, or no treatment in the reduction of ANV, both in severity and duration. Dobkin (1987) showed that SD could be used to reduce, or maybe even prevent, posttreatment nausea and vomiting.

EMG Biofeedback

Biofeedback refers to a number of procedures that provide information to a subject about one or more biological responses (Masters et al., 1987). Electromyographic (EMG) biofeedback is often used as a general relaxation technique. Most EMG biofeedback procedures involve attaching three small electrodes to the forehead to measure tension levels primarily from the muscles in the upper facial area. The general purpose of biofeedback is to teach a person to use the feedback to gain conscious control of a biological response over which the subject previously had little or no control.

Burish, Shartner and Lyles (1981) used EMG biofeedback combined with relaxation to treat a 44 year old female cancer patient with both ANV and posttreatment nausea and vomiting. After ten training sessions the patient was able to reduce her physiological arousal (EMG, pulse rate, and blood pressure) and reported feeling less nauseated.

Stimulus Control

The conditioning model of ANV suggests that stimulus control might be an effective treatment. Manipulations that disrupt the predictive relationship between the conditioned stimulus and the unconditioned stimulus should allow the conditioned nausea and vomiting to extinguish, and it should also be possible to eliminate ANV by

removing or significantly altering the stimuli assumed to elicit the conditioned response (Greene & Seime, 1987).

Greene and Seime (1987) employed a stimulus control technique on a 61 year old female with intraductal breast cancer, using a masking stimulus (lemon juice) to obscure taste sensations thought to function as a conditioned stimulus. A decrease in ANV was observed across the course of six chemotherapy treatments.

Stress Inoculation Training

Stress inoculation is aimed at helping clients cope with aversive states by enhancing their self-control skills. Stress inoculation training involves three relatively discrete phases: education, acquisition (often including PRT), and application (Masters et al., 1987). There is evidence that stress inoculation training is useful in dealing with phobic reactions (Meichenbaum & Cameron, 1972), general states of chronic overarousal, and stress (Long, 1985; Lustman & Sowa, 1983).

Moore and Altmaier (1981) used a stress inoculation training package, involving cognitive behaviour modification combined with PRT and education, to treat nine cancer patients. Consequently, three patients reported feeling less anxious prior to treatment, having learned effective coping skills.

Mode of Action

Four hypotheses have been proposed to explain how and why behaviour therapy is effective for treating both anticipatory and posttreatment nausea and vomiting in cancer chemotherapy patients:

(1) Nonspecific Factors - Factors such as attention received from a therapist, demand characteristics, expectation for success, or other 'placebo' effects may be involved in the effectiveness of behaviour therapy. From the available evidence, however, it seems that, although these factors may play a role, other treatment components are necessary for the therapy to be effective (Morrow, 1982; Morrow & Dobkin, 1988).

(2) Cognitive Diversion - This hypothesis states that behaviour therapy diverts the patient's attention away from the chemotherapy treatments so that the conditioning no longer occurs - removing the conditioned stimuli prevents the occurrence of the conditioned response. The cognitive diversion hypothesis is also inconsistent with the

available evidence, in that the availability of distracting stimuli (e.g. television, friends and family) has failed to reduce the side effects of chemotherapy. It should also be noted that systematic desensitisation actually focuses attention on these stimuli but still has the ability to reduce the side effects as much as hypnosis and progressive relaxation training (Morrow & Dobkin, 1988).

(3) Self-Control - This proposes that behavioural techniques change the patient's self-perceived sense of control over their disease. As their psychological state improves their subjective feeling of helplessness diminishes, resulting in less nausea and vomiting as they feel they are 'in control' of their cancer and its treatment. As yet there is no empirical evidence to support this hypothesis and only one study that provides any evidence against it (Morrow & Morrell, 1982).

(4) Relaxation - It has been suggested that the key ingredient in all of the behavioural techniques is the induction of a relaxed state - which consequently leads to a reduction in anxiety and physiological arousal (Burish & Carey, 1984; Redd & Andrykowski, 1982). Morrow (1986) suggests that relaxation may be a necessary but not sufficient treatment component for reducing ANV. This study also suggests that counterconditioning is a necessary element in the treatment package. Counterconditioning involves the pairing of a conditioned stimulus with an unconditioned stimulus or conditioned stimulus that elicits a different or incompatible response to the one which it is currently conditioned with, counteracting the effects of the original conditioning process.

The Therapist's Role

The amount of therapist time needed to carry out the treatments described above is quite large, and is a major consideration when deciding whether a patient should receive behaviour therapy to reduce or prevent ANV. The possible use of audio tapes to reduce the necessary professional time required to administer treatments such as hypnosis and systematic desensitisation has been investigated, but it has been found that the voice on the tape has become a conditioned stimulus, eliciting nausea (Morrow, 1984; Redd, Rosenberger & Hendler, 1983). Another possible way of reducing the therapist time required is to instruct other health professionals (nurses and physicians) in the

administration of behaviour therapy. There is some evidence to support this solution, showing that behaviour therapy techniques can be taught to a variety of health professionals and still be effective, and that physicians and nurses may be as credible as psychologists in the use of these procedures (Morrow & Dobkin, 1987).

Summary of the Psychological Treatments

All of the psychological treatment methods appear to provide control of, and/or protection from, the development of anticipatory symptoms. It is unclear exactly how these treatments work, although relaxation and cognitive diversion appear to be the two most important components. The use of these psychological treatments is not limited to trained therapists and it is possible for them to be taught to and used effectively by a variety of health professional without losing their effectiveness.

Aims of This Study

The main aims of this study are to assess the prevalence of anticipatory nausea and vomiting in a setting where 5-HT_3 receptor antagonists are widely used; to confirm any relationships there may be between the development of anticipatory symptoms and various demographic, clinical, and psychological variables; and to uncover any other factors which may increase the likelihood of a cancer chemotherapy patient developing anticipatory nausea and vomiting.

Assuming that the learning model for the development of ANV is correct, a reduction in posttreatment nausea and vomiting should prevent or delay the acquisition of anticipatory symptoms. Therefore, given that 5-HT_3 receptor antagonists are currently the most effective pharmacological treatments for chemotherapy induced emesis, it is hypothesised that the prevalence of anticipatory nausea and vomiting should be lower than the prevalence rates reported in studies where 5-HT_3 receptor antagonists have not been used. As there have been no studies reporting the prevalence of anticipatory nausea and vomiting where 5-HT_3 receptor antagonists have been used as the main antiemetic, the prevalence rates from all other studies on anticipatory nausea and vomiting may be used as a comparison. The prevalence of ANV in this study should therefore be less than, or at least at the lower end of the range of prevalence rates reported previously, which is generally 20-40% (Bernstein, 1991).

Another important part of the study is the examination of the relationships which have been shown to exist between ANV and various demographic, clinical, and psychological variables. The demographic factors of gender and age will be examined, with age having shown a consistent relationship with ANV in the past and gender having only shown a significant relationship in a small percentage of studies. The younger patients, under 50 years old, are expected to have a higher incidence of ANV (Morrow & Dobkin, 1988; Burish & Carey, 1986). If there is a relationship between gender and the development of ANV, previous research would suggest that the females in the study should experience a higher incidence of ANV than the males (Fetting et al., 1983; Wilson et al., 1986).

The clinical variables which will be examined are the frequency and severity of posttreatment nausea and vomiting, the patients current susceptibility and history of motion sickness, and the emetogenicity of the chemotherapy protocols. It is hypothesised that those patients who experience more severe and frequent posttreatment nausea and vomiting will be more likely to develop ANV than those patients who experience only mild and occasional posttreatment nausea and vomiting (Morrow & Dobkin, 1988). Those patients who are susceptible to motion sickness are expected to experience more posttreatment nausea and vomiting and therefore will be more likely to develop ANV (Morrow, 1984; 1985; Leventhal et al., 1988). Also related to posttreatment nausea and vomiting is the hypothesis that those patients who are receiving the most emetogenic chemotherapy regimens will experience more posttreatment nausea and vomiting and will have a high prevalence of ANV.

The accuracy of the emetogenicity predictions will be tested by comparing the predicted nausea and vomiting with the actual nausea and vomiting which accompanies the chemotherapy protocols in this study. This will provide some indication of how accurate the medical staffs' perception of the nausea and vomiting associated with chemotherapy is, and may also give an indication of how effective the new antiemetics are in controlling the expected nausea and vomiting. The results of this investigation should also provide some guidelines for the estimation of the emetogenicity of chemotherapy protocols - providing information for the selection of appropriate antiemetic cover.

The psychological variables which will be measured and examined in this study are: state anxiety, trait anxiety, and depression levels before receiving each cycle of chemotherapy; and the patient's expectations about the side effects which he or she may encounter as a result of his or her chemotherapy.

State anxiety has almost always been shown to have a positive relationship with ANV (Morrow & Dobkin, 1988), so it is expected to be higher in the patients who develop ANV. The results should reveal whether higher levels of state anxiety are present before the development of ANV and posttreatment nausea and vomiting, or if state anxiety increases after the development of ANV and posttreatment nausea and

vomiting. The relationship between trait anxiety and ANV has never produced any consistent results in the past, although when a significant relationship has been reported it has always been that trait anxiety is higher in patients who develop ANV. Also of interest is whether state anxiety and trait anxiety remain stable over time.

Some level of depression in cancer patients is expected (Cavanaugh & Wettstein, 1989), but there have been reports that higher than normal levels of depression are related to the development of ANV (Morrow & Dobkin, 1988). This study aims to provide some information about the relationship which exists between depression and ANV. The change in the levels of depression over time will also be of interest.

The patients' expectations about the side effects which may accompany their chemotherapy will also be measured. This should reveal whether the patients' expectations have any influence on the development of ANV and posttreatment nausea and vomiting. Currently there has been no consistent relationship found between ANV and the expectations of the patient, although one study has reported that higher expectations are correlated with a higher incidence of ANV and posttreatment nausea and vomiting (Andrykowski & Redd, 1987).

Chapter II

METHOD

Patients

SELECTION CRITERIA AND PROCEDURES

Potential participants for this study were recruited from the Oncology Department at Christchurch Hospital between the 26th of April and the 13th of September, 1993. Each new patient who fitted the following criteria for inclusion was approached to obtain informed consent to participate.

Criteria for Inclusion:

1) Eighteen years or older.

2) Receiving cyclical chemotherapy.

3) No previous chemotherapy.

4) No pre-existing nausea or vomiting due to brain metastases or gastrointestinal involvement by cancer.

5) Able to give informed consent.

Each patient was given an information sheet (Appendix 2) which outlined the aims and procedures of the study and any questions that the patient had about the study were answered before consent to participate was obtained.

This study received ethical approval from the University of Canterbury and Christchurch Hospital before any patients were approached.

Procedures

ENVIRONMENT

The oncology department at Christchurch Hospital services a large portion of the South Island of New Zealand. The outpatient department had a chemotherapy suite situated on the first floor, which contained four recliner chairs and two hospital beds. The chemotherapy is usually administered by one of two specialist nurses who staff this suite on a regular basis. The oncology department is associated with an oncology ward located in the main hospital, which is about five minutes walk from the oncology department. This ward is staffed by nurses who have a great deal of experience in administering chemotherapy. Whenever possible, those patients who are receiving very emetic chemotherapy regimens are placed in one of the single rooms available in this ward.

The majority of the interviewing for those receiving their chemotherapy as outpatients in this study was conducted in a consultation room near the chemotherapy suite. The interview room contained a desk, some chairs, a hand-basin, an x-ray light, a white board and a large cupboard. The three patients who were instructed in progressive muscle relaxation training were taken through the procedure in an examination room adjoining the interview room. The relaxation training room contained a bed, wardrobe, chair and bedside cabinet.

Most of the interviewing for those receiving their treatment as inpatients was conducted in the oncology ward, at the bedside. This was often in a four or five-bed room with other patients around at the time of the interview. Some patients were assigned to single rooms and were interviewed in this much more private environment.

INITIAL INTERVIEW

Most of the initial interviews, before the patient had received his/her first cycle of chemotherapy, were conducted in the interview room in the oncology department; and the balance were conducted in the oncology ward. Each patient completed the questionnaires in the initial interview under supervision and with assistance from the investigator. The questionnaires for this initial interview were completed in the following order for each patient: 1) Side Effect Expectancy Questionnaire, 2) Susceptibility to motion sickness, 3) Anxiety and Depression Visual Analogue Scales, 4) State-Trait Anxiety Inventory, and 5) Beck Depression Inventory. Three patients, numbers 002, 019 and 022, did not want to complete the Side Effect Expectancy Questionnaire as they did not want to think they were starting their treatment with expectations about any side effects which they may or may not experience. Two patients (001 and 002) did not complete the visual analogue scale questionnaire during their initial interview as this questionnaire was not available at the time of their interviews.

The timing of this initial interview was always planned so that it was completed within the three hours preceding their first chemotherapy treatment. These interviews typically lasted approximately thirty minutes, but in some cases where the patient was extremely unwell or tired the interview lasted for up to one hour from start to finish.

This extra time was necessary as these patients often needed to take a break during the interview and most of these patients required the investigator to present everything verbally.

PRETREATMENT ASSESSMENT

Each patient was required to complete three questionnaires before day one of each of their chemotherapy cycles. The questionnaires were always completed in the following order: 1) Anxiety and Depression Visual Analogue Scales, 2) State-Trait Anxiety Inventory and 3) Beck Depression Inventory. Most patients preferred to complete the questionnaires themselves after being guided through them for the first one or two cycles, although some patients preferred to complete all of their questionnaires under supervision. The pretreatment interviews typically lasted about twenty minutes for those who required supervision and only a few minutes for those who preferred to complete the questionnaires themselves; after which they would take the questionnaires away to complete while waiting for their chemotherapy.

POSTTREATMENT ASSESSMENT

The Morrow Assessment of Nausea and Emesis was completed at least seven days, but never more than twenty-eight days, after the patients had completed each cycle of chemotherapy. Most of these assessments were completed in telephone interviews, although sometimes they were completed while the patient was back at the hospital between treatments (for example, during radiotherapy appointments for those patients being treated for breast cancer). For the patients who were receiving weekly or two-weekly infusions, the nausea and vomiting assessments were conducted prior to the pretreatment interview for their next cycle of chemotherapy.

REVIEWING OF PATIENT NOTES

While they were participating in the study, each patient's medical and oncology notes were periodically reviewed to obtain information regarding their medical status,

antiemetic cover, and general well-being. The investigator was also in regular contact with the patients' oncologists and other medical staff who dealt with the patients.

PROGRESSIVE MUSCLE RELAXATION TRAINING (PMRT)

The progressive muscle relaxation training method used in this study closely followed Cormier and Cormier's (1979) procedure. PMRT involves learning how to relax by actively tensing and relaxing various muscle groups in a progressive manner. This relaxation training procedure requires that the subject be as comfortable as possible - preferably wearing comfortable clothing and in a comfortable environment. The ideal situation would be a small room with a recliner chair for the subject to lie back in, but for the purposes of this study a small clinical examination room adjoining the interview room was used. The patient was asked to lay on the bed in this room and to get as comfortable as possible before starting the relaxation training procedure. The initial training session lasted 30-45 minutes and all other training sessions took about 20 minutes.

PMRT was offered to all patients who had experienced anticipatory nausea or vomiting on two consecutive cycles (Patients 001, 002, 004, and 007), apart from the two patients being treated for testis cancer who developed anticipatory nausea (Patients 014 and 018), as they had finished their treatment by the time they had experienced two consecutive cycles of anticipatory nausea. Of the four patients who were offered PMRT, only patient 007 thought that her anticipatory symptoms were bad enough to try using relaxation training.

Overall, three patients in this study were instructed in progressive muscle relaxation training. Patient 007 developed severe anticipatory nausea before the second half of her third cycle and was offered PMRT before receiving her next cycle of chemotherapy. She was guided through the procedure for cycles four and the first half of cycle five, after which her anticipatory symptoms were no longer present and she thought it was no longer necessary to go through the relaxation procedure before her next cycles. Patient 017 was told about the relaxation training which was being offered to those patients who developed anticipatory nausea and vomiting, and consequently wanted to be shown the

procedure before she started her first cycle of chemotherapy. She was instructed in PMRT for her first two cycles but then discontinued the training due to personal problems and a back complaint which made the exercises uncomfortable. Patient 020 also requested to be shown PMRT before cycle one and also acquired a relaxation tape from another source before starting treatment. He was instructed in PMRT for his first two cycles and then continued to use his relaxation tape for the remainder of his chemotherapy cycles. The results of the relaxation training are provided in Appendix 3, as this was not a major part of the study.

Measures

BECK DEPRESSION INVENTORY (BDI)

The Beck Depression Inventory (BDI) was first introduced in 1961 (Beck et al., 1961). The revised version of the BDI was developed in 1971 and copyrighted in 1978 (Beck et al., 1979). It has become one of the most widely used instruments for assessing the intensity of depression in psychiatric patients and also for detecting depression in normal populations (Beck, Steer & Garbin, 1988).

The Beck Depression Inventory was used in this study to provide a measure of the level of depression prior to each chemotherapy cycle. It was chosen over other tools, such as the Hospital Anxiety and Depression Scale, as it provides two measures - the first thirteen items cover the affective/cognitive symptoms of depression and the remaining eight items cover the physiological symptoms of depression.

Description

The content of the BDI was derived from clinical observations about the attitudes and symptoms displayed frequently by depressed psychiatric patients and infrequently by non-depressed psychiatric patients (Beck et al., 1961). These clinical observations were consolidated into twenty-one symptoms and attitudes which could be rated from zero to three in terms of intensity. The twenty-one items are: 1)Mood, 2)Pessimism, 3)Sense of Failure, 4)Lack of Satisfaction, 5)Guilt Feelings, 6)Sense of Punishment, 7)Self-dislike, 8)Self-accusation, 9)Suicidal Wishes, 10)Crying, 11)Irritability, 12)Social Withdrawal, 13)Indecisiveness, 14)Distortion of Body Image, 15)Work Inhibition, 16)Sleep

Disturbance, 17)Fatigability, 18)Loss of Appetite, 19)Weight Loss, 20)Somatic Preoccupation, 21)and Loss of Libido.

Forms

The BDI was originally intended for clinical administration but a card form is now available (May, Urquhart & Tarran, 1969), as are several computerised forms which have been developed to join the original paper-and-pencil self-administered form. There have been no direct comparisons among these forms to estimate whether or not the format affects its reliability and validity. There is also a short form of the BDI (Beck & Beck, 1972), but although the long and short forms are highly correlated there is evidence that the short form may represent one cognitively oriented symptom dimension, where as the long form represents non-cognitive symptom clusters also (Beck, Steer & Garbin, 1988). The long form was used in this study as it essentially contains two measures, one being the affective and cognitive symptoms of depression and the other being the physiological symptoms of depression.

Versions

There have been two major versions developed:

1) Beck, Ward ,Mendelson, Mack and Erbaugh (1961)

2) Beck, Rush, Shaw and Emery (1979)

It is notable that many researchers seem unaware that there are two versions of the BDI, with many publications not stating which version was used or only mentioning one version when in fact it was the other version which they used. The two versions are considered to be highly correlated (Lightfoot & Oliver, 1985). It was the later version which was used in this study.

Administration

It appears to make no difference in the respondents' scores as to whether or not the BDI is administered publicly or privately (King & Buchwald, 1982). However, the gender of the administrator may influence the responses, with same-gender administrators leading to scores which are likely to be one point higher (King & Buchwald, 1982). However, Bryson and Pilon (1984) reported no gender difference. The

BDI was administered both publicly and privately in the current study, and the investigator was a 23 year old male psychology masters student.

Scoring

The BDI is scored by adding the scores for each of the 21 items to obtain a total score and also a score for the affective/cognitive symptoms (items 1-13) and the physiological symptoms (items 14-21). The maximum total score is 63, with a maximum of 39 for the affective/cognitive items and 24 for the physiological items.

Reliability and Validity

The BDI has been shown to have high internal consistency (Beck, Steer, & Garbin, 1988) and stability (Beck, 1967). It also has high content validity, reflecting six of the nine DSM-III criteria satisfactorily (Moran & Lambert, 1983); and also high concurrent validity with clinical ratings, the Hamilton Psychiatric Rating Scale for Depression, the Zung Self-Reported Depression Scale, the MMPI Depression Scale, and the Multiple Affect Adjective Checklist Depression Scale (Beck, Steer, & Garbin, 1988). The BDI has also demonstrated high discriminant validity, with the ability to differentiate depressed and alcoholic patients from normals (Conde & Esteban, 1976), psychiatric patients from normals (Akiskal et al., 1982), and also the ability to detect depression in medical patients (Rhodes, 1981; Sullivan, 1979; Turner & Romano, 1984). The items in the BDI have demonstrated good construct validity, with BDI scores being related to biological indicators of depression such as REM latency (Akiskal et al., 1982) and plasma 11-hydroxycorticosteroids (Brooksbank & Coppen, 1967).

Demographic Correlates

1) Gender - there is conflicting evidence about the correlation between the gender of the respondent and their BDI score. However, more studies have reported that women have higher BDI scores than men, although several other studies have reported no significant relationship between gender and BDI scores.

2) Age - Adolescents have been reported to score higher than adults (Levine, 1982; Teri, 1982) and the elderly tend to score higher than younger respondents (Schnurr et al., 1976).

3) Education - Educational attainment has been shown to be inversely related to BDI scores (Beck, 1967; Dorus & Senay, 1980).

4) Race - there is no clear relationship between race and BDI scores.

Norms and Clinical Cut-offs

The Center for Cognitive Therapy has distributed the following guidelines for BDI cut-off scores: none or minimal depression = <10; mild to moderate depression = 10-18; moderate to severe depression = 19-29; and severe depression = 30-63. Beck and Beamesderfer (1974) stated that scores of 13-20 indicate mild depression, 21-30 indicate moderate depression, and 31 or greater indicate severe depression. Norris et al. (1987) used a cut-off score of 17 to detect major depression in medical outpatients. Also, Craven et al. (1988) used a cut-off score of 14/15 to detect minor depression in renal dialysis patients, and a cut-off score of 12/13 was found to be 79% sensitive and 77% specific by Neilson and Williams (1980) to define the lower limits of depression in a medical population.

A mean BDI score of 13.9 (S.D. 8.2) was reported for cancer patients compared to a significantly lower mean score of 11.1 (S.D. 9.0) for patients with other medical disorders (Cavanaugh & Wettstein, 1989). Cavanaugh and Wettstein (1989) also report that cancer patients have significantly higher scores on the physiological symptoms of the BDI, with a mean score of 5.8 (S.D. 5.7) on the affective/cognitive symptoms and a mean score of 8.1 (S.D. 4.0) on the physiological symptoms. The same study also reports that 51.2% of the cancer patients recorded BDI scores ≥13 and 15.6% recorded BDI scores ≥21. For the purposes of determining clinical significance in this study, the cut-off scores provided by the Center for Cognitive Therapy will be used to determine the level of clinical depression for each BDI score.

Use of the BDI in Medical Populations

The BDI has been used extensively in medical populations in a wide variety of studies and is reported to be as good at detecting depression in these patients as any other self-report screening method (Meakin, 1992). Zich et al. (1990) suggest that the BDI might assist physicians in reliably detecting depression in medical patients as they demonstrated a high level of agreement between the BDI and the DSM-III diagnosis of a

major depressive episode. A comparison among various medical populations shows that patients with gastrointestinal disease, cancer, bone and connective tissue disease, neurological disease, and respiratory disease have the greatest amount of depressive symptomatology (Cavanaugh & Wettstein, 1989; Cavanaugh, 1986). It has also been demonstrated that the BDI works equally as well with medical patients as it does with psychiatric patients (Emmons, Fetting, & Zonderman, 1987). So although the BDI has not previously been used to measure levels of depression in anticipatory nausea and vomiting studies, there is no reason why its use here should be questioned.

SPEILBERGER STATE-TRAIT ANXIETY INVENTORY (STAI)

The construction of the STAI began in 1964 in an attempt to develop a single set of items that could be administered with different instructions to provide objective measures of state and trait anxiety.

Trait anxiety refers to relatively stable individual differences in anxiety proneness, that is, to differences between people in the tendency to perceive stressful situations as dangerous or threatening and to respond to such situations with elevations in the intensity of their state anxiety. Trait anxiety may also reflect individual differences in the frequency and intensity with which anxiety states have been manifested in the past, and in the probability that state anxiety will be experienced in the future. The stronger the trait anxiety, the more probable that the individual will experience more intense elevations in state anxiety in a threatening situation.

The State-Trait Anxiety Inventory was used in this study to provide a measure of the level of state and trait anxiety before each chemotherapy cycle. It was used in preference to other measures of anxiety as it provides measures for both state and trait anxiety and it has been used extensively in similar research.

Description

The STAI (Speilberger et al., 1983) was designed to measure state and trait anxiety in college and high school students and has since been used extensively in research and clinical practice. The inventory consists of twenty statements that evaluate how respondents feel 'right now' (Form Y-1), and twenty statements that assess how

respondents 'generally' feel (Form Y-2), yielding separate scores for state and trait anxiety respectively. The twenty items of the STAI-S are: 1) Calm, 2) Secure, 3)Tense, 4)Strained, 5)At ease, 6)Upset, 7)Worrying over possible misfortunes, 8)Satisfied, 9)Frightened, 10)Comfortable, 11)Self-confident, 12)Nervous, 13)Jittery, 14)Indecisive, 15)Relaxed, 16)Content, 17)Worried, 18)Confused, 19)Steady, 20)Pleasant. The twenty items of the STAI-T are: 21)Pleasant, 22)Nervous and restless, 23)Satisfied with self, 24)Wish could be as happy as others seem to be, 25)Feel like a failure, 26)Rested, 27)Calm, cool, and collected, 28)Difficulties piling up and cannot overcome them, 29)Worry too much over something that really doesn't matter, 30)Happy, 31)Disturbing thoughts, 32)Lack self-confidence, 33)Secure, 34)Make decisions easily, 35)Feel inadequate, 36)Content, 37)Unimportant thoughts run through mind, 38)Take disappointments so keenly that can't put them out of mind, 39)Steady, 40)Get in state of tension or turmoil as think over recent concerns and interests.

Scoring

Each item in the STAI is given a weighted score of 1 to 4. A rating of 4 indicates the presence of a high level of anxiety for ten state anxiety items and eleven trait anxiety items. A high rating indicates the relative absence of anxiety for the remaining ten state anxiety items and nine trait anxiety items. The scoring weights for the anxiety-present items are the same as the numbers on the test form (i.e. items 1, 2, 5, 8, 10, 15, 16, 19, 20, 21, 23, 26, 27, 30, 33, 34, 36, 39) whereas the scoring weights for the remaining anxiety-absent items are the reverse of the numbers on the test form (i.e. 1, 2, 3, 4 are scored as 4, 3, 2, 1). To obtain the scores for state anxiety and trait anxiety, you add the weighted scores for the first twenty items to obtain the state anxiety score and add the weighted scores for the other twenty items to obtain the trait anxiety score. Scores for both the state anxiety and trait anxiety scales can vary from a minimum of 20 to a maximum of 80.

Reliability: Stability and Internal Consistency

A median test-retest correlation coefficient for the trait anxiety scale when used with college and high school students has been reported as 0.765 and 0.695 respectively (Speilberger et al., 1983). The state anxiety scale has inherently low test-retest stability,

as a valid measure of state anxiety should reflect the influence of unique situational factors that exist at the time of testing and which result in fluctuations in respondents' test scores over time. The state anxiety scale does, however, exhibit high internal consistency with a median alpha coefficient of 0.93 being reported (Speilberger et al., 1983) . A median alpha coefficient of 0.90 has been reported for the trait anxiety scale (Speilberger et al., 1983).

Validity

1) Contrasted Groups - There is evidence to show that the STAI-T score can discriminate between normals and psychiatric patients, with psychiatric patients demonstrating significantly higher trait anxiety scores (Speilberger et al., 1983). Evidence of construct validity comes from the observation that the scores of military recruits tested shortly after beginning highly stressful training programs were much higher than those of college and high school students of about the same age who were tested under relatively non-stressful conditions (Speilberger et al., 1983).

2) Correlations Between the State Anxiety and Trait Anxiety Scales - Persons high in trait anxiety tend to be higher in state anxiety, even in relatively neutral situations. This correlation is decreased under stressful conditions and increased under conditions that pose some threat to self-esteem (Speilberger et al., 1983).

Norms

The norms provided in the STAI manual are not always appropriate, being based on a large sample of college undergraduates and high school students in the United States, and smaller groups of male psychiatric patients, general medical and surgical patients, and young prisoners, also from the United States. Therefore, Knight, Waal-Manning and Spears (1983) conducted a study on 1173 subjects from a small town in the South Island of New Zealand. The average state anxiety score was 30.19 (S.D:7.31) for males and 33.51 (S.D:8.61) for females; whereas the average trait anxiety score was 33.11 (S.D:7.80) for the males and 36.85 (S.D:8.89) for the females. There is some trend for both the state anxiety and trait anxiety scores to correlate with age, with the younger subjects recording higher scores (Knight et al., 1983).

The Use of the STAI in Medical Populations

The STAI has been used extensively in much of the research on anticipatory nausea and vomiting (e.g. van Komen & Redd, 1985; Andrykowski et al., 1985, 1987; Andrykowski, 1988), and also in a recent study on anticipatory anxiety in cancer chemotherapy patients (Jacobsen, Bovjberg, & Redd, 1993).

MORROW ASSESSMENT OF NAUSEA AND EMESIS (MANE)

The MANE was designed by Morrow (1982) in an attempt to provide a reliable and valid tool for the assessment of chemotherapy treatment-related nausea and vomiting. Currently the MANE is the most comprehensive and widely used measure of treatment-related nausea and vomiting (Carnrike et al., 1988).

Description

The MANE is a brief 16-item questionnaire which assesses the frequency, severity and duration of pretreatment and posttreatment nausea and vomiting associated with previous chemotherapy. The first eight items on the questionnaire assess the duration and severity of posttreatment nausea and vomiting as well as assessing when the nausea and vomiting were at their worst. The next six items assess the severity of pretreatment nausea and vomiting and also how long before the treatment it first occurred. The last two items on the questionnaire assess how useful the patient thought his/her medication was in controlling the nausea and vomiting.

Reliability and Validity

The MANE has been found to have a high degree of reliability on the severity and duration of treatment-related nausea and vomiting (Morrow, 1984). It has also demonstrated a moderate degree of test-retest reliability, although it appears to be more reliable with respect to nausea than vomiting (Carnrike et al., 1988). Carnrike et al. (1988) also report that the MANE has a moderate degree of concurrent validity, although they also report a nonsignificant level of discriminant validity. This nonsignificant level of discriminant validity relates to the high correlation between items within the MANE.

The MANE was used in this study as it is currently the most reliable and valid tool for assessing both posttreatment and pretreatment nausea and vomiting.

SIDE EFFECT EXPECTANCY QUESTIONNAIRE (SEEQ)

The Side Effect Expectancy Questionnaire was developed specifically to assess patient expectations for experiencing each of 16 side effects associated with chemotherapy (Appendix 4; Andrykowski & Redd, 1987). For each side effect, patients indicated their expectations on a 5-point categorical scale. The patients were told before they were shown the SEEQ that it contained a list of the side effects associated with all of the different chemotherapy drugs and that it was not a list of the side effects associated with their chemotherapy in particular. The sixteen side effects which it lists are: nausea, vomiting, tiredness, hair loss, nervousness, change in taste or appetite, weight loss, weight gain, skin itching, pain, weakness, diarrhoea, sleep problems, chills, problems with sex, and constipation. It takes about five minutes to complete. The SEEQ is scored by adding the scores for each of the sixteen side effects to obtain a total, with a possible maximum score of 80.

The SEEQ has been used in studies on anticipatory nausea and vomiting in cancer chemotherapy patients (Andrykowski & Redd, 1987); and a similar questionnaire, with only thirteen side effects, was used recently in a study looking at anticipatory anxiety associated with cancer chemotherapy (Jacobsen, Bovbjerg, & Redd, 1993). The SEEQ was used in this study to determine whether there is a relationship between the amount of side effects the patient is expecting and the level of posttreatment and pretreatment nausea and vomiting which that patient experiences.

SUSCEPTIBILITY TO MOTION SICKNESS

The patients were assessed as to their history of motion sickness during the initial interview and the results from this were recorded by the interviewer in the space provided at the bottom of the SEEQ (Appendix 4). Information was obtained as to their current susceptibility to motion sickness and how sensitive they were, as well as a general history of their susceptibility to motion sickness.

DEPRESSION & ANXIETY 10CM VISUAL ANALOGUE SCALES

In order to provide some sort of verification of the levels of anxiety and depression being reported on the Beck Depression Inventory and the State-Trait Anxiety Inventory, a very brief, three item questionnaire was constructed (Appendix 5). Ten centimetre visual analogue scales have been used to measure pretreatment anxiety (Jacobsen, Bovbjerg, & Redd, 1993) and depression in cancer chemotherapy patients previously.

Description

On the one page questionnaire there are three 10cm visual analogue scales; one each for state anxiety, trait anxiety and depression. The patients were instructed to make a mark along each of the 10cm lines. For the first item, they were instructed to place a mark on the line which corresponded to the level of anxiety that they were experiencing 'now'. The second item was to indicate how anxious the patient is 'generally', and the third item was answered as to how depressed the patient was feeling with no reference to any time period. The entire questionnaire took approximately one minute to complete each time, although it often took five or ten minutes to explain how to complete the questionnaire during the initial interview.

Scoring

The answers were scored by measuring from the left-hand end of the lines to the patients' marks, yielding a score in millimetres.

e.g. A mark at this point on the visual analogue scale would yield a score of 45mm.

Statistical Analysis

For the purposes of analysing the data, the patients were divided into two groups, one being the patients who developed anticipatory nausea and/or vomiting (ANV group) and the other containing the patients who did not experience anticipatory nausea and/or vomiting (non-ANV group).

Averages were obtained for each patient at each cycle and population standard deviations were used to compare these averages. Student t-tests (two-tailed, for independent means) were used to test for any significant differences between the two groups on all of the variables measured. No other tests of statistical significance were used due to the low number of subjects and the correspondingly low level of power which they would have. The relationship between variables was tested using Pearson product-moment correlation coefficients and the trend of the data was tested using simple linear regression analysis. An alpha value of 0.05 was used for all tests.

Chapter III

RESULTS

Patient Variables

PARTICIPANTS

Of the thirty-six patients who fitted the criteria for inclusion in the study, twenty-six (72%) were approached and successfully enlisted; six (17%) were deemed unsuitable by their oncologist, either because they were only expected to receive one or two treatments or due to their emotional state; three (8%) refused to participate; and one (3%) was missed due to confusion about when she was to start her treatment. Patient 012 died soon after receiving his first cycle of chemotherapy and was consequently excluded from all statistical analyses.

Table 3.
Demographics for Individual Patients

Pat. No.	*Age*	*Gender*	*Diagnosis*	*Extent*
1	36	m	Sarcoma	Metastatic
2	40	f	CA Breast	Stage II
3	58	m	NHL	Invaded distal spermatic cord
4	53	f	CA Breast	Metastatic
5	61	f	NHL	Stage IIIa
6	67	m	NHL	Intermediate grade, diffuse large cell
7	20	f	HD	Nodular sclerosing
8	51	f	Ovarian	Stage II-III
9	69	f	Ovarian	Stage II
10	67	f	Adeno.Colon	Dukes C
11	41	f	CA Breast	Stage I
12	65	m	Myeloma	Kidney metastases
13	54	m	Adeno.Colon	Dukes C2
14	34	m	Teratoma Testis	Stage I
15	44	m	Seminoma Testis	Large retroperitoneal mass
16	69	m	Adeno.Colon	Dukes C
17	39	f	CA Breast	Stage II
18	28	m	Teratoma Testis	Stage II
19	59	m	HD	Stage IIIb
20	25	m	HD	Stage Ib
21	42	m	Germ Cell Testis	Stage I
22	55	f	Myeloma	
23	41	m	HD	Stage II
24	40	m	NHL	Stage II
25	65	m	Adeno.Colon	Dukes C
26	46	f	CA Breast	Stage III

HD=Hodgkin's Disease, Adeno.Colon=Adenocarcinoma of the Colon, NHL=Non-Hodgkin's Lymphoma, CA=Carcinoma.

GENDER

As Table 3 shows, fourteen (56%) of the patients analysed in this study were male and eleven (44%) were female. Of the six (24%) patients who developed ANV, three (50%) were male and three (50%) were female. In the non-ANV group which contained nineteen patients, eleven (58%) were male and eight (42%) were female.

AGE

The average age of all of the participants was 43.72 (SD:14.2). The average age of those patients who went on to develop ANV was 35.17 (SD:11.2), significantly lower than the average age of those who did not develop ANV, 52.26 (SD:12.6; $t(23)=-2.9661$, $P<0.01$). Table 4 shows that the patients with Hodgkin's Disease, Testis, and Breast Carcinoma were younger than those with non-Hodgkin's lymphoma, myeloma, colon and ovarian cancer. The average ages for the different diagnostic groups are generally representative of the general age of patients receiving chemotherapy for these types of cancer.

DIAGNOSIS

Table 4.
Diagnosis and Age of the Patients Analysed

	Number	Mean Age (s.d)	Number (%) With ANV
Sarcoma	1	36	1 (100%)
Adeno.Colon	4	63.75 (6.70)	0 (0%)
CA Breast	4	43.80 (5.81)	2 (50%)
NHL	4	56.50 (11.62)	0 (0%)
HD	4	36.25 (17.61)	1 (25%)
Myeloma	2	60.00 (7.07)	0 (0%)
Ovarian	2	60.00 (12.73)	0 (0%)
Testis	4	37.00 (7.39)	2 (50%)
Total	25*	43.72 (14.2)	6 (24%)

*Patient number 012 died after cycle one, so only twenty five patients were analysed

Table 3 shows the demographics for all of the patients in the study and Table 4 shows the average age of patients in the different diagnostic groups. Four patients were treated for non-Hodgkin's lymphoma; three males and one female, with an average age of 56.50 (SD:11.62). Five patients were treated for carcinoma of the breast; all female, with an

average age of 43.80 (SD:5.81). Four patients were treated for Hodgkin's Disease; three males and one female, with an average age of 36.25 (SD:17.61). Four males were treated for testis cancer; with an average age of 37.00 (SD:7.39). Four patients were treated for colon cancer; three males and one female, with an average age of 63.75 (SD:6.70). Two females, one 52 years old and the other 69 years old, were treated for ovarian cancer. Two patients, a 65 year old male and a 56 year old female, were treated for myeloma. One 37 year old male was treated for sarcoma.

CHEMOTHERAPY PROTOCOLS

Of the five patients treated for carcinoma of the breast, one received six cycles of intravenous Cyclophosphamide and Adriamycin, and oral Prednisone (CAP), and the other four patients received either six or eight cycles of intravenous Cyclophosphamide, Methotrexate, and 5-FU (CMF). All five patients had their chemotherapy recycled every four weeks.

Two of the four patients treated for non-Hodgkin's lymphoma received intravenous Cyclophosphamide, Adriamycin and Vincristine, and oral Prednisone (CHOP), plus intra-thecal Methotrexate. One of these patients received four cycles and the other six cycles. The patient who received four cycles had his dose reduced to 75% of his initial dose for cycles three and four. One of the remaining two lymphoma patients received six cycles of intravenous Cyclophosphamide, Etoposide and Vincristine, and oral Prednisone (CHOP with the adriamycin replaced by etoposide due to the patient's cardiac history); and the other received six cycles of CHOP. All four of the patients with non-Hodgkin's lymphoma had their chemotherapy recycled every four weeks.

Two of the Hodgkin's Disease patients received six cycles of intravenous Adriamycin, Bleomycin, Vinblastine, and Dacarbazine (ABVD). This protocol involved receiving ABVD on day one and fifteen of each cycle, and having their treatment recycled on day 28. One received only two cycles of ABVD before being changed to oral Chlorambucil, intravenous Vinblastine, oral Procarbazine, and oral Prednisone (ChlVPP) for the remaining four cycles due to a pre-existing heart problem which made the continued use of Adriamycin inadvisable. The remaining HD patient received six

cycles of ChlVPP. The patients receiving ChlVPP had their chemotherapy recycled every four weeks.

All four of the patients with testis cancer received four cycles of intravenous Bleomycin, Etoposide, and Cisplatin (BEP), although the bleomycin was removed from the last couple of cycles in most of these patients due to its effects on their respiratory functioning. The testis cancer patients had their chemotherapy recycled every three weeks.

The four patients with colon cancer all received five consecutive days of intravenous 5-FU followed by six months of weekly intravenous 5-FU plus fortnightly oral Levamisole.

Both of the patients with ovarian cancer were treated with intravenous Carboplatin every four weeks. One received three cycles and the other received four cycles before their diseases were found to have progressed and one had her treatment changed to Taxol and the other had her treatment discontinued.

Two patients with myeloma received intravenous Cyclophosphamide every four weeks.

One patient with sarcoma received intravenous Adriamycin on two consecutive days, every three weeks. The dose was spread over two days due to its cardiotoxicity.

A detailed list of the chemotherapy protocols used on the patients in this study is provided in appendix 6.

ANTIEMETIC COVER

The antiemetic cover provided for each patient during each of their chemotherapy cycles is listed in Table 5. Sixteen (64%) of the twenty-five patients were given 5-HT_3 receptor antagonists at cycle one, with eighteen (72%) patients receiving either ondansetron or granisetron for the majority of their chemotherapy cycles. All but one (83%) of the ANV patients received 5-HT_3 receptor antagonists throughout their chemotherapy, and the remaining patient received ondansetron from her second cycle onwards. Most of the patients receiving 5-HT_3 antagonists, and some who were receiving metoclopramide, were prescribed dexamethasone as well as ondansetron or

granisetron. One patient was part of a study looking at the efficacy of providing five days cover with ondansetron, but was returned to the standard dose schedule after her second cycle of chemotherapy. The patients who did not receive 5-HT_3 receptor antagonists were all given metoclopramide for any nausea or vomiting which they experienced.

FOLLOW-UP PERIOD

Table 6 shows the number of cycles for which each of the twenty-six patients were followed. Twenty-four patients were followed for at least four cycles of their chemotherapy. Patient number 012 died two days after receiving his first cycle of chemotherapy due to complications from his kidney disease and patient number 008 was followed for only three cycles, at which point her disease was found to have progressed and her chemotherapy was discontinued. For the purposes of conducting an analysis of the results, the data from patient 008 was included but the data collected from patient 012 was not included in any statistical analyses.

Of the twenty-four patients who were followed for four cycles or more, thirteen were followed for four cycles, one was followed for five cycles, eight for six cycles, one for seven, and one for eight cycles of their chemotherapy.

The average number of cycles for which a patient was followed and assessed was 5.06 (range 3-8); 5.33 (range 4-6) for those who developed ANV and 4.79 (range 3-8) for the non-ANV patients ($t(23)=0.9220$, ns).

Table 5.
Antiemetic Cover Provided During Each Chemotherapy Cycle (C)

Patient	*Antiemetic Cover*
1	C1: Ondansetron, C2-6: Ondansetron+Dexamethasone
2	C1-2: Ondansetron+Dexamethasone, C3-4: Granisetron, C5-6: Granisetron+Dexamethasone
3	C1-6: Ondansetron+Dexamethasone
4	C1: Metoclopramide+Dexamethasone, C2-6: Ondansetron+Dexamethasone
5	C1-6: Ondansetron+Dexamethasone
6	C1: Metoclopramide+Dexamethasone, C2-4: Ondansetron+Dexamethasone
7	C1-6: Ondansetron+Dexamethasone
8	C1-3: Ondansetron
9	C1-4: Metoclopramide+Dexamethasone
10	C1-8: Metoclopramide

Table 5. (Contd)

Patient	*Antiemetic Cover*
11	C1-3: Ondansetron+Dexamethasone, C3-6: Granisetron+Dexamethasone
13	C1-5: Metoclopramide
14	C1: Granisetron, C2-4: Granisetron+Dexamethasone
15	C1-4: Granisetron+Dexamethasone
16	C1-7: Metoclopramide
17	C1-2: Ondansetron, C3: Ondansetron+Dexamethasone, C4-6: Granisetron+Dexamethasone
18	C1-4: Granisetron+Dexamethasone
19	C1-4: Metoclopramide
20	C1-4: Ondansetron+Dexamethasone
21	C1-4: Granisetron+Dexamethasone
22	C1-4: Metoclopramide
23	C1-4: Ondansetron
24	C1-4: Ondansetron+Dexamethasone
25	C1-4: Metoclopramide
26	C1-2: Ondansetron 5 Day Trial*, C3-4: Ondansetron

*This patient received a five day supply of ondansetron for her first two cycles of chemotherapy.
Ondansetron=Zofran 8mgPOx3
Granisetron=Kytril 3mgIVx1
Metoclopramide=Maxolon 10-20mgIV or PO
Dexamethasone=8-16mgIV or PO

SUSCEPTIBILITY TO MOTION SICKNESS

Table 6 shows that fifteen (60%) of the twenty-five patients who were included in the statistical analyses did not presently suffer from motion sickness, four (16%) suffered only from sea sickness, and six (24%) suffered from motion sickness in general. Four (16%) of these patients did not presently suffer from motion sickness but reported experiencing motion sickness earlier in their lives.

Of the ANV patients, four (66%) did not presently suffer from motion sickness, one (17%) suffered from sea sickness, and one (17%) suffered from motion sickness in general. One (17%) of the ANV patients did not presently suffer from motion sickness but reported experiencing motion sickness as a child. In the non-ANV group, twelve (58%) did not presently suffer from motion sickness, three (16%) suffered from sea sickness, and five (26%) suffered from motion sickness in general. Three (15%) of the non-ANV patients did not presently suffer from motion sickness but reported experiencing it in the past. These similar percentages for both groups indicate that there was no clear relationship between the patients' susceptibility to motion sickness and the development of ANV.

Table 6.
Cycles Followed and Motion Sickness History

Patient Number	No. of Cycles Followed	Motion Sickness
1	6	No
2	6	No
3	6	No
4	6	Childhood
5	6	Pregnancy
6	4	No
7	6	No
8	3	Sea
9	4	Yes
10	8	20 yrs ago
11	6	Yes
13	5	No
14	4	Sea
15	4	Childhood
16	7	No
17	6	Yes
18	4	Yes
19	4	No
20	4	Yes
21	4	No
22	4	No
23	4	Sea
24	4	No
25	4	Sea
26	4	Yes

Posttreatment Nausea and Vomiting

Posttreatment nausea and vomiting were assessed using the Morrow Assessment of Nausea and Emesis. Separate severity ratings, from 1-6 (Very Mild-Intolerable), were obtained for posttreatment nausea and posttreatment vomiting. The frequency of the posttreatment nausea and vomiting was obtained by calculating the percentage of cycles in which nausea and vomiting were reported on the MANE for each patient.

POSTTREATMENT NAUSEA AND VOMITING SEVERITY

Table 7 shows the average severity of posttreatment nausea experienced by all of the patients analysed, as well as showing the ANV patients and non-ANV patients separately.

Table 7.
Posttreatment Nausea Severity

	All Patients	ANV	Non-ANV
Cycle 1	1.62	2.67 (n=6)	1.29 (n=19)
Cycle 2	1.74	2.92 (n=6)	1.37 (n=19)
Cycle 3	1.46	3.08 (n=6)	0.95 (n=19)
Cycle 4	1.77	3.67 (n=6)	1.14 (n=18)
Cycle 5	0.77	1.38 (n=4)	0.43 (n=7)
Cycle 6	1.85	2.88 (n=4)	1.17 (n=6)
Cycle 7	0.50	*	0.50 (n=2)
Cycle 8	2.00	*	2.00 (n=1)
Average	1.58	2.97	1.14
S.D.	1.47	1.49	1.16
Highest	2.50	4.25	1.95
Lowest	0.78	1.92	0.42

*no patients who developed ANV were followed for more than six cycles.

The average severity level of posttreatment nausea in the ANV group was 2.97 (SD:1.49; 'Moderate' on the MANE), which is significantly higher than the average of 1.14 (SD:1.16; 'Very mild' on the MANE) for the patients in the non-ANV group ($t(23)=3.8062$, $P<0.01$). The ANV group had a higher average level of posttreatment nausea for all six of the cycles comparable - significantly higher on all but the fifth cycle. The ANV group were 0.94 standard deviations higher after cycle one ($t(23)=2.3190$, $P<0.05$), 1.05 SDs higher after cycle two ($t(23)=2.4005$, $P<0.05$), 1.45

SDs higher after cycle three (t(23)=3.2552, P<0.01), 1.72 SDs higher after cycle four (t(22)=4.3627, P<0.01), and 1.16 SDs higher after cycle six (t(8)=2.6431, P<0.05); but only 0.65 SDs higher after cycle five (t(9)=1.7904, ns).

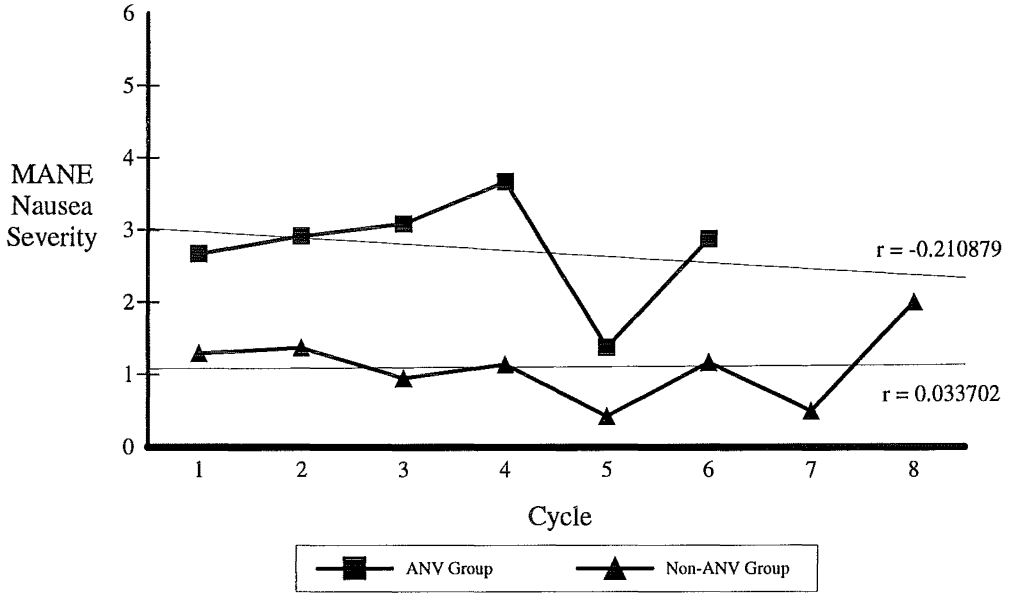

Figure 2. *Posttreatment Nausea Severity*

The most severe posttreatment nausea was reported by the ANV group, and was 126% higher than that reported by the non-ANV group on average (t(23)=3.7847, P<0.01), and the lowest levels reported by the non-ANV group were 79% lower than those reported by the patients in the ANV group (t(23)=3.2049, P<0.01).

Figure 2 shows that the severity of posttreatment nausea in the ANV group reached a peak following cycles three and four, whereas the non-ANV group remained relatively stable over the first six cycles. The regression lines and corresponding correlation coefficients indicate that the relationship between posttreatment nausea severity and the cycle number is nonlinear, with a relatively flat regression lines (ANV group: slope=-0.09, Non-ANV group: slope=0.01) and low levels of correlation (ANV group: r=-0.21, Non-ANV group: r=0.03). It appears that the level of posttreatment nausea in the ANV group increased gradually over the first four cycles, but then dropped sharply for the fifth cycle before increasing again after the sixth cycle.

Table 8.
Posttreatment Vomiting Severity

	All Patients	ANV	Non-ANV
Cycle 1	0.58	1.92 (n=6)	0.16 (n=19)
Cycle 2	0.68	1.67 (n=6)	0.37 (n=19)
Cycle 3	1.22	2.58 (n=6)	0.79 (n=19)
Cycle 4	1.13	2.83 (n=6)	0.56 (n=18)
Cycle 5	0.64	1.00 (n=4)	0.43 (n=7)
Cycle 6	1.00	1.50 (n=4)	0.67 (n=6)
Cycle 7	0.00	*	0.00 (n=2)
Cycle 8	0.00	*	0.00 (n=1)
Average	0.86	2.14	0.46
S.D.	1.33	1.57	0.95
Highest	1.78	3.75	1.16
Lowest	0.24	0.83	0.05

*no patients who developed ANV were followed for more than six cycles.

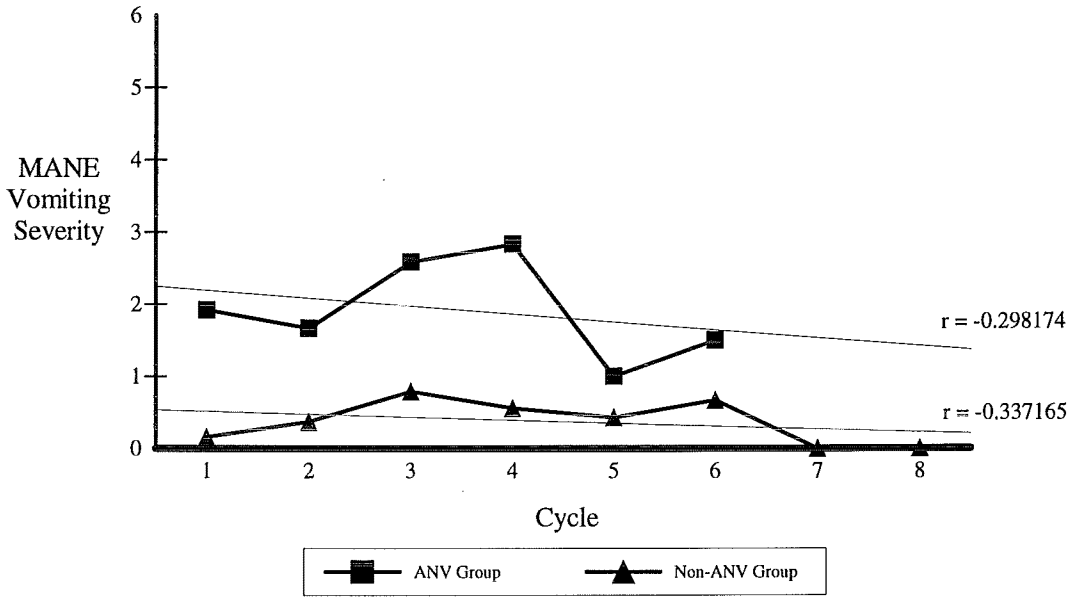

Figure 3. *Posttreatment Vomiting Severity*

Similarly, the average posttreatment vomiting severity level reported by those in the ANV group of 2.14 (SD:1.57; Mild on the MANE), was significantly higher than the average level of 0.46 (SD:0.95; less than Very mild on the MANE) reported by those in the non-ANV group ($t(23)=4.5672$, $P<0.01$). Table 8 shows that the ANV group consistently rated their posttreatment nausea higher than the patients in the non-ANV

group, being significantly higher after the first four cycles; 1.32 standard deviations higher at cycle one ($t(23)=4.1613$, $P<0.01$), 0.95 SDs higher at cycle two ($t(23)=2.8506$, $P<0.01$), 1.35 SDs higher at cycle three ($t(23)=2.7581$, $P<0.05$) and 1.71 SDs higher at cycle four ($t(22)=4.3393$, $P<0.01$). The difference was not significant for the fifth and sixth cycles; being only 0.43 SDs higher at cycle five ($t(9)=0.6900$, ns) and 0.62 SDs higher at cycle six ($t(8)=0.9035$, ns). The highest average levels of the ANV group were 217% higher than those of the non-ANV group ($t(23)=4.2291$, $P<0.01$), and the lowest average levels of the non-ANV group were 87% lower than those of the ANV group ($t(23)=2.5565$, $P<0.05$).

Figure 3 shows that the severity of posttreatment vomiting in the two groups reached a peak following cycles three and four. The regression lines and corresponding correlation coefficients indicate that the relationship between posttreatment vomiting severity and the cycle number is nonlinear, with a relatively flat regression lines (ANV group: slope=0.11, Non-ANV group: slope=-0.04) and low levels of correlation (ANV group: r=-0.30, Non-ANV group: r=-0.34). Figure 3 also shows that both groups demonstrated the same pattern - starting out with less severe vomiting, developing their worst vomiting after cycles three and four, and then experiencing less severe posttreatment vomiting after cycles five and six.

POSTTREATMENT NAUSEA AND VOMITING FREQUENCY

As Figure 4 shows, the patients in the ANV group reported posttreatment nausea 94% of the time whereas the patients in the non-ANV group reported posttreatment nausea 56% of the time ($t(23)=2.4043$, $P<0.05$). Table 10 shows that four (21%) patients in the non-ANV group experienced no nausea at all but there were no patients in the ANV group who experienced complete control of their posttreatment nausea. Those patients in the non-ANV group who did not have complete control of their posttreatment nausea experienced it 72% of the time.

Figure 4 also shows that the patients who developed ANV reported posttreatment vomiting 69% of the time whereas those who did not develop ANV reported posttreatment vomiting 23% of the time ($t(23)=3.2167$, $P<0.01$). Table 10 shows that

ten of the patients in the non-ANV group did not experience any vomiting at all but there were no patients in the ANV group who experienced complete control of their posttreatment vomiting. Those patients in the non-ANV group who did not have complete control of their posttreatment vomiting experienced posttreatment vomiting 47% of the time.

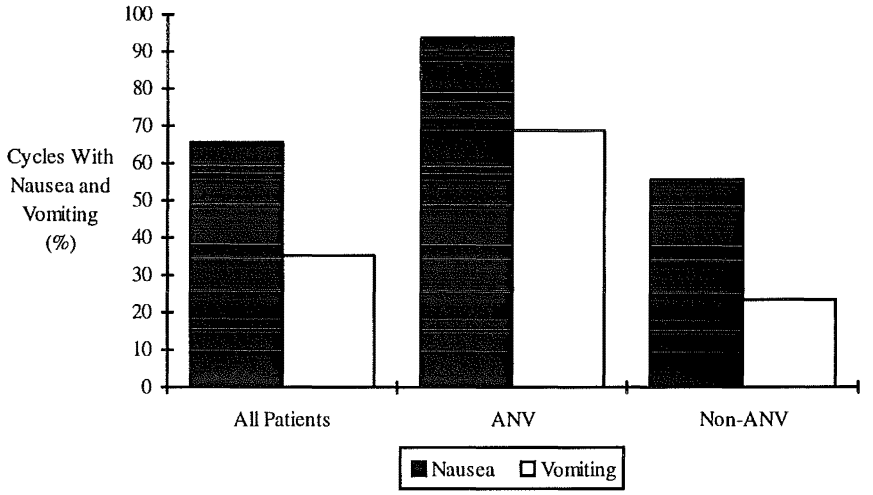

Figure 4. *Frequency of Posttreatment Nausea and Vomiting*

As Figure 5 shows, age demonstrated a large negative relationship with posttreatment nausea (r=-0.58), indicating that younger patients experienced more posttreatment nausea than older patients. This relationship was not as strong with posttreatment vomiting (r=0.25). There was a very strong correlation between posttreatment nausea severity and posttreatment nausea frequency (r=0.84), as well as a strong correlation between posttreatment vomiting severity and posttreatment vomiting frequency (r=0.93). This means that a higher frequency of posttreatment nausea and vomiting corresponded to a higher severity of posttreatment nausea and vomiting, so that the patients who experienced posttreatment nausea and vomiting more often were also the patients who experienced the most severe nausea and vomiting. Also, there was a high correlation between posttreatment nausea severity and posttreatment vomiting severity (r=0.62), and between posttreatment nausea frequency and posttreatment vomiting frequency (r=0.41). This shows that the patients who experienced more severe nausea also experienced more severe vomiting, and that patients who experienced posttreatment nausea more often also experienced posttreatment vomiting more often. Table 9 shows

that there were no large differences in the severity of posttreatment nausea and vomiting experienced by the male and female patients.

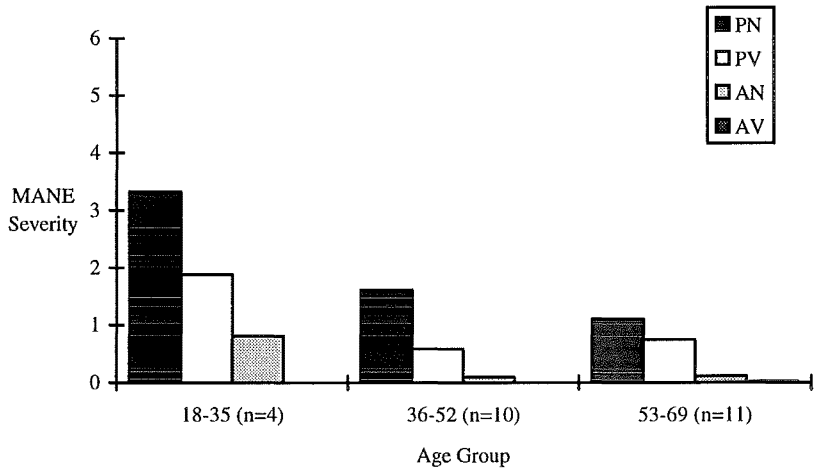

Figure 5. *Posttreatment and Pretreatment Nausea and Vomiting for Three Age Groups*

Table 9.
Posttreatment and Pretreatment Vomiting Severity for Males and Females

	Male (n=14)	Female (n=11)
Posttreatment Nausea	1.60	1.60
Posttreatment Vomiting	0.83	1.13
Pretreatment Nausea	0.20	0.27
Pretreatment Vomiting	0	0.02

Table 10.
Frequency of Posttreatment Nausea and Vomiting

Patient	**Posttreatment Nausea Frequency (% of cycles)**	**Posttreatment Vomiting Frequency (% of cycles)**
1	67	100
2	100	17
3	0	0
4	100	83
5	83	33
6	100	75
7	100	33
8	33	0
9	50	50
10	63	13
11	100	50
13	60	0
14	100	100
15	25	0
16	0	0
17	80	100

Table 10. (Contd)

Patient	Posttreatment Nausea Frequency (% of cycles)	Posttreatment Vomiting Frequency (% of cycles)
18	100	100
19	50	0
20	75	0
21	50	0
22	0	50
23	100	0
24	100	0
25	0	25
26	100	50
All	66	35
ANV	94	69
Non-ANV	56	23

EXPECTED VERSUS ACTUAL NAUSEA AND VOMITING

Tables 11 and 12 show the expected frequency and severity of nausea and vomiting for all of the patients in the study. The actual posttreatment nausea and vomiting severity scores (PNS and PVS) are the average nausea and vomiting ratings from the MANE, which yields a severity rating from 1-6 (Very Mild-Intolerable). The actual posttreatment nausea and vomiting frequency ratings (PNF and PVF) were calculated using the percentages from Table 10, giving a frequency rating from 0-4 (Never-Always). For example, patient 001 experienced posttreatment nausea after 67% of his chemotherapy cycles, so his frequency rating is 67% of 4, or 2.67. The expected nausea and vomiting, frequency and severity ratings, were obtained from the results of the 'Toxicity Questionnaire' mentioned in the introduction. Unfortunately, in comparing the actual nausea and vomiting versus the expected nausea and vomiting it is not possible to make a direct comparison as they are on different scales, although they are both measuring the same variable in a similar manner. The expected nausea and vomiting ratings are in two groups, one being the expected nausea and vomiting where the most emetic substance (Max) in the protocol is used to calculate the emetogenicity of the entire protocol, and the other being the expected nausea and vomiting where the average emetogenicity (Mean) of all of the components in the protocol are used.

Tables 11 and 12 show that the patients who developed ANV were expected, on average, to experience nausea and vomiting more often and more severe than the

patients who did not develop ANV, and that this was true for both methods of estimating protocol emetogenicity (Max:$t(23)=2.0999$, $P<0.05$; Mean:$t(23)=2.1441$, $P<0.05$). The ANV group were also expected to experience more severe nausea and vomiting as a result of their chemotherapy, and this was also consistent using both methods of estimation (Max:$t(23)=2.1593$, $P<0.05$; Mean:$t(23)=2.3730$, $P<0.05$).

Reasonably good correlations existed between posttreatment nausea severity and expected severity estimated using the most emetic substance ($r=0.49$), and between posttreatment nausea frequency and expected frequency estimated using the most emetic substance ($r=0.49$). The correlations between the estimates using the average emetogenicity and the actual nausea and vomiting were comparatively low. This shows that the most accurate estimate of the emetogenicity of the chemotherapy protocols was obtained using the most emetic substance as the basis for the estimation and not the average emetogenicity of all of the drugs in the protocol.

Table 11.

Expected Versus Actual Posttreatment Nausea

Patient	Actual PNS* (1-6)	Actual PNF* (0-4)	Expected Frequency (Max) (0-4)	Expected Severity (Max) (1-3)	Expected Frequency (Mean) (0-4)	Expected Severity (Mean) (1-3)
1	1.50	2.67	3	2.4	3	2.4
2	2.83	4	2	1.5	1.3	1.17
3	0	0	2	1.5	1.175	0.95
4	1.67	4	3	2.4	1.77	1.37
5	1.00	3.33	3	2.4	1.525	1.225
6	3.25	4	3	2.4	1.4	1.16
7	3.83	4	3.3	2.5	2.1	1.725
8	0.33	1.33	2.3	1.7	2.3	1.7
9	1.00	2	2.3	1.7	2.3	1.7
10	1.25	2.5	1	1.1	0.75	0.8
11	2.17	4	2	1.5	1.3	1.17
13	1.40	2.4	1	1.1	0.75	0.8
14	4.75	4	3.7	2.9	2.07	1.67
15	0.50	1	3.7	2.9	2.07	1.67
16	0	0	1	1.1	0.75	0.8
17	1.80	3.2	2	1.5	1.3	1.17
18	3.25	4	3.7	2.9	2.07	1.67
19	0.50	2	1.2	1.2	0.85	0.75
20	1.50	3	3.3	2.5	2.1	1.725
21	0.50	2	3.7	2.9	2.07	1.67
22	0	0	2	1.5	2	1.5
23	2.50	4	3.3	2.5	2.1	1.725
24	2.25	4	3	2.4	1.4	1.16
25	0	0	1	1.1	0.75	0.8
26	1.75	4	2	1.5	1.3	1.17
All	1.58	2.62	2.46	1.97	1.61	1.34
ANV	2.97	3.78	3.12	2.43	2.05	1.67
Non-ANV	1.14	2.25	2.25	1.82	1.48	1.24

*PNS=Posttreatment Nausea Severity, PNF=Posttreatment Nausea Frequency

Table 12.
Expected vs Actual Posttreatment Vomiting

Patient	Actual PVS* (1-6)	Actual PVF* (0-4)	Expected Frequency (Max) (0-4)	Expected Severity (Max) (1-3)	Expected Frequency (Average) (0-4)	Expected Severity (Average) (1-3)
1	2.00	4	3	2.4	3	2.4
2	0.67	0.67	2	1.5	1.3	1.17
3	0	0	2	1.5	1.175	0.95
4	2.67	3.33	3	2.4	1.77	1.37
5	0.50	1.33	3	2.4	1.525	1.225
6	2.25	3	3	2.4	1.4	1.16
7	1.00	1.33	3.3	2.5	2.1	1.725
8	0	0	2.3	1.7	2.3	1.7
9	0.75	2	2.3	1.7	2.3	1.7
10	0.38	0.5	1	1.1	0.75	0.8
11	0.83	2	2	1.5	1.3	1.17
13	0	0	1	1.1	0.75	0.8
14	3.50	4	3.7	2.9	2.07	1.67
15	0	0	3.7	2.9	2.07	1.67
16	0	0	1	1.1	0.75	0.8
17	1.60	4	2	1.5	1.3	1.17
18	3.00	4	3.7	2.9	2.07	1.67
19	0	0	1.2	1.2	0.85	0.75
20	0	0	3.3	2.5	2.1	1.725
21	0	0	3.7	2.9	2.07	1.67
22	1.50	2	2	1.5	2	1.5
23	0	0	3.3	2.5	2.1	1.725
24	0	0	3	2.4	1.4	1.16
25	0.25	1	1	1.1	0.75	0.8
26	0.75	2	2	1.5	1.3	1.17
All	0.87	1.41	2.46	1.97	1.61	1.34
ANV	2.14	2.89	3.12	2.43	2.05	1.67
Non-ANV	0.46	0.94	2.25	1.82	1.48	1.24

*PVS=Posttreatment Vomiting Severity, PVF=Posttreatment Vomiting Frequency

Anticipatory Nausea and Vomiting

Six (24%) of the twenty-five patients developed ANV while they were participating in this study. Five (83%) of the ANV patients developed anticipatory nausea and one (17%) experienced both anticipatory nausea and anticipatory vomiting. Two patients (011 and 017) experienced anticipatory anxiety and loss of appetite but did not report anticipatory nausea or vomiting.

A severity rating from 1-6 (Very Mild-Intolerable) was obtained for anticipatory nausea and anticipatory vomiting. The frequency of the anticipatory nausea and vomiting was obtained by calculating the percentage of cycles in which anticipatory nausea and vomiting were reported for each patient and translating that percentage into a rating from 0-4 (Never-Always).

PRETREATMENT NAUSEA AND VOMITING SEVERITY

Table 13 shows that the average severity of the anticipatory nausea experienced by the six patients who developed ANV was 0.93 (SD:1.13), which corresponds to 'mild' on the MANE. There was only one episode of 'very mild' anticipatory vomiting, experienced by patient 004, before her fourth cycle of chemotherapy. As Figure 6 shows, the worst anticipatory nausea was experienced prior to cycles three and four, with considerably higher levels of AN reported before these cycles. The highest level of AN reported was 'moderate' and was reported at some stage by five out of the six patients who developed ANV. There was little or no anticipatory nausea reported prior to cycles five and six.

There was a reasonably good negative correlation between the severity of the anticipatory nausea and the age of the patient (r=-0.46), so that the younger patients experienced more anticipatory nausea than the older patients. Also, posttreatment nausea severity was shown to have a reasonable correlation with anticipatory nausea severity (r=0.44), showing that more severe posttreatment nausea is associated with more severe anticipatory nausea.

Table 13.
Pretreatment Nausea and Vomiting Severity

	Pretreatment Nausea	Pretreatment Vomiting
Cycle 1 (n=6)	0.50	0.00
Cycle 2 (n=6)	0.50	0.00
Cycle 3 (n=6)	1.83	0.00
Cycle 4 (n=6)	1.83	0.17
Cycle 5 (n=4)	0.25	0.00
Cycle 6 (n=4)	0.00	0.00
Average	0.93	0.03
S.D.	1.13	0.07
Highest	2.67	0.17

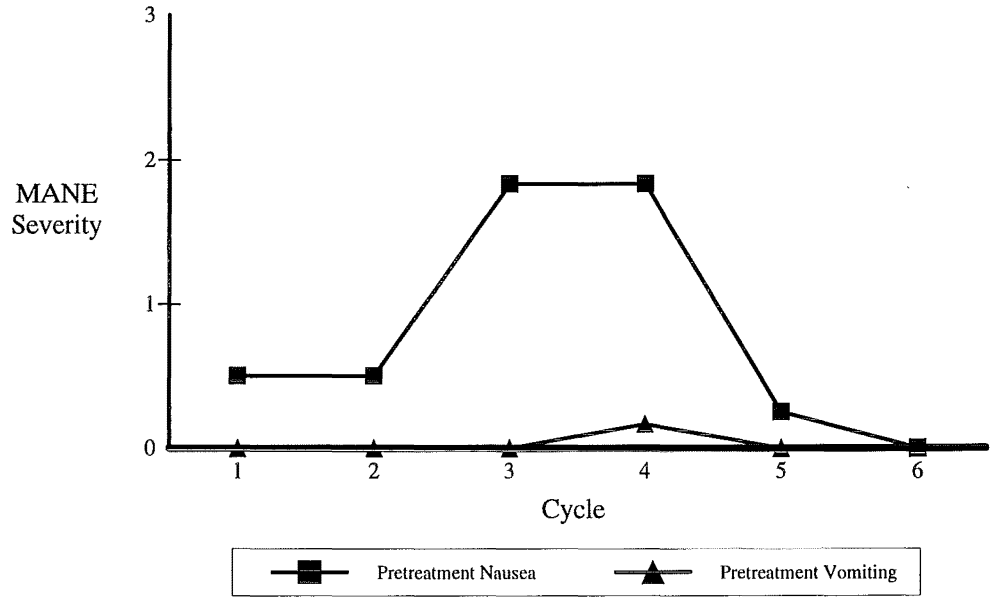

Figure 6. *Pretreatment Nausea and Vomiting Severity*

PRETREATMENT NAUSEA AND VOMITING FREQUENCY

One (17%) of the ANV patients experienced AN prior to receiving her first treatment, two (33%) developed ANV prior to their second cycles of chemotherapy, two (33%) experience AN for the first time prior to their third cycles, and one (17%) developed AN prior to receiving his fourth cycle of chemotherapy. The patient who experienced anticipatory nausea before her first treatment had received radiotherapy for her breast cancer about four years prior to this and had experienced a great deal of nausea and vomiting during that treatment, consequently making her very anxious about starting chemotherapy.

Table 14 shows the percentage of cycles in which the six ANV patients experienced anticipatory nausea and vomiting. Patient 001 experienced anticipatory nausea for the last three of his six cycles of Adriamycin; patient 002 experienced anticipatory nausea prior to cycles two and three but not again during her six cycles of CMF chemotherapy; patient 004 experienced anticipatory nausea prior to receiving her first four treatments of CAP chemotherapy and also reported 'very mild' anticipatory vomiting prior to her fourth cycle; patient 007 reported experiencing anticipatory nausea prior to her second, third and fourth cycles of ABVD; and patients 014 and 018 experienced anticipatory nausea before their last two out of four cycles of BEP. On average, the patients who experienced anticipatory nausea reported it before 47% of their treatments. Three patients reported anticipatory nausea before half of their treatments, two reported it before one third of their treatments, and one patient reported it before two thirds of her treatments.

Posttreatment nausea severity was shown to have a positive relationship with anticipatory nausea frequency (r=0.54), showing that more severe posttreatment nausea is associated with more frequent episodes of anticipatory nausea. There was a very strong correlation between anticipatory nausea severity and anticipatory nausea frequency (r=0.90), which shows that more severe anticipatory nausea is very closely linked with more frequent episodes of anticipatory nausea. This means that the patients who experience the most severe anticipatory nausea also experience anticipatory nausea more often. Also, there were reasonably strong correlations between anticipatory nausea severity and expected severity using the most emetic substance (r=0.44), and also between anticipatory nausea frequency and expected frequency using the same method of estimation (r=0.43). This demonstrates that the expected emetogenicity of the protocols (using the most emetic substance) was a reasonably good predictor of the severity and frequency of anticipatory nausea.

Table 14.

Frequency of Pretreatment Nausea and Vomiting

Patient	Pretreatment Nausea Frequency (% of cycles)	Pretreatment Vomiting Frequency (% of cycles)
1	33	0
2	33	0
4	67	17
7	50	0
14	50	0
18	50	0
Total	47	3

Psychological Factors

STATE ANXIETY

A) STAI-S Scores

The STAI-State anxiety scores for those who developed ANV and those who did not develop ANV were compared. On average, the patients who developed ANV scored significantly higher on this measure of state anxiety ($t(23)=3.1065$, $P<0.01$). The average score for the ANV group over the entire follow-up period was 37 (SD:9.58), 28% higher than the average score for the non-ANV group of 29 (SD:7.03). Table 15 shows that the average STAI-S scores of the ANV group were consistently higher than those of the non-ANV group and were significantly higher on the first three cycles; 1.40 standard deviations higher at cycle one ($t(23)=3.1921$, $P<0.01$), 0.94 SDs higher at cycle two ($t(23)=2.5886$, $P<0.05$) and 1.22 SDs higher at cycle three ($t(23)=2.5902$, $P<0.05$). There was no significant difference for the last three cycles; only 0.67 SDs higher at cycle four ($t(22)=1.4132$, ns), 0.92 SDs higher at cycle five ($t(9)=1.8173$, ns) and 0.10 SDs higher at cycle six ($t(8)=0.1969$, ns). On average the ANV group recorded maximum scores 31% higher than patients in the non-ANV group ($t(23)=3.1267$, $P<0.01$), whereas the non-ANV groups' lowest scores were 19% less than those in the ANV group ($t(23)=2.0293$, ns).

The regression lines in Figure 7 show that there is a large downward trend for the ANV group (slope=-2.60) and that this line accurately reflects the pattern of results (r=-0.89). So, as the patients proceeded through their chemotherapy they reported a decreasing level of state anxiety before each cycle. The non-ANV group did not demonstrate this general decline in state anxiety - remaining relatively stable throughout their chemotherapy (slope=0.17), although the flat line does not accurately represent the pattern of results (r=0.17).

The younger patients tended to report higher levels of state anxiety (r=-0.44). Overall, there was a strong correlation between the STAI-State scores and the STAI-Trait scores (r=0.72), although the relationship was stronger in the non-ANV patients (r=0.70) compared to the ANV patients (r=0.54). This correlation shows that the STAI-Trait anxiety scores were influenced by the STAI-State scores and vice versa, so that a

higher state anxiety score was correlated with a high trait anxiety score. There was a reasonable correlation between the STAI-S scores and the state anxiety mm scores overall (r=0.48), but there was only a good correlation among the ANV group. This shows that the visual analogue scale state anxiety scores provided a good validation of the state anxiety scores measured using the STAI, but only in the ANV group. There were strong correlations between the STAI-S scores and posttreatment nausea (r=0.65) and vomiting (r=0.64) severity, and also between STAI-S scores and posttreatment nausea (r=0.63) and vomiting (r=0.53) frequency. This means that high state anxiety score were associated with more severe and frequent posttreatment nausea and vomiting. The STAI-S scores were also closely related to anticipatory nausea severity (r=0.63) and frequency (r=0.61), showing that high levels of state anxiety were associated with more severe and frequent anticipatory nausea..

STAI-State scores were also shown to be highly predictive of the occurrence of anticipatory nausea in consequent cycles. STAI-S scores at cycle one were highly correlated with anticipatory nausea severity before cycle two (r=0.84) and cycle three (r=0.85). So, the patients who had high levels of state anxiety at cycle one were likely to have more severe anticipatory nausea before cycles two and three. There was an opposite relationship between STAI-S scores at cycle two and anticipatory nausea severity at cycle three (r=-0.70), but a positive relationship between STAI-S scores at cycle two and anticipatory nausea severity at cycle four (r=0.51). This means that the patients with high state anxiety at cycle two experienced less severe anticipatory nausea at cycle three and more anticipatory at cycle four. There was a very high positive correlation between STAI-S scores at cycle three and anticipatory nausea severity at cycle four (r=0.91), with patients who having high state anxiety at cycle three experiencing high levels of anticipatory nausea at cycle four.

In comparison to the norms for the STAI-S reported by Knight, Waal-Manning and Spears (1983) of 30.19 (S.D:7.31) for males and 33.51 (S.D:8.61) for females, the average for the males was 31.15 (SD:8.47) and the average for the females was 31.14 (SD:8.48).

Table 15.
State-Trait Anxiety Inventory, State Anxiety Averages

	All Patients	ANV	Non-ANV
Cycle 1	34.98	43.92 (n=6)	32.16 (n=19)
Cycle 2	30.26	36.25 (n=6)	28.37 (n=19)
Cycle 3	31.38	39.17 (n=6)	28.92 (n=19)
Cycle 4	30.19	34.42 (n=6)	28.78 (n=18)
Cycle 5	29.68	34.63 (n=4)	26.86 (n=7)
Cycle 6	27.15	27.63 (n=4)	26.83 (n=6)
Cycle 7	33.00	*	33.00 (n=2)
Cycle 8	32.00	*	32.00 (n=1)
Average	31.15	37.36	29.19
S.D.	8.41	9.58	7.03
Highest	38.32	46.75	35.66
Lowest	25.50	29.75	24.16

*no patients who developed ANV were followed for more than six cycles.

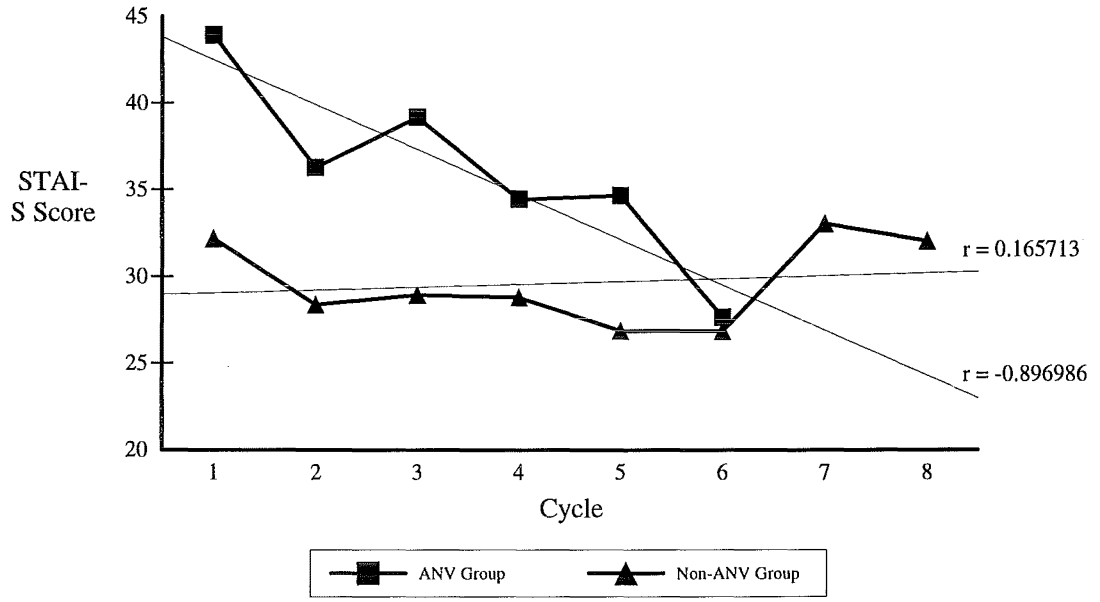

Figure 7. *STAI-State Anxiety Averages*

B) STAI-S Profiles

Although the ANV patients scored higher on average on the STAI-S than non-ANV patients, they did not score significantly higher on all of the STAI-S items. Figure 8 and Table 16 show that the ANV patients, on average, scored significantly higher on nine of the twenty items. The items which were significantly higher in the ANV group were items 2 (Secure; t(23)=2.5125, P,0.05), 3 (Tense; t(23)=2.2845, P<0.05), 5 (At ease;

t(23)=2.2150, P,0.05), 13 (Jittery; t(23)=2.9258, P<0.01), 15 (Relaxed; t(23)=2.1993, p<0.05), 16 (Content; t(23)=2.3187, P<0.05), 18 (Confused; t(23)=2.6104, P<0.05), 19 (Steady; t(23)=3.6596, P<0.01), and 20 (Pleasant; t(23)=2.3695, P<0.05). The items which were not significantly different were 1 (Calm), 4 (Strained), 6 (Upset), 7 (Worried about possible misfortunes), 8 (Satisfied), 9 (Frightened), 10 (Comfortable), 11 (Self-confident), 12 (Nervous), 14 (Indecisive), and 17 (Worried). The patients who developed ANV were less secure, more tense, less at ease, more jittery, less relaxed, less content, more confused, less steady, and feeling less pleasant than those patients who did not develop ANV.

Table 16.

State-Trait Anxiety Inventory - State Anxiety Individual Item Averages

Item	Average All Pats	Average ANV	Average Non ANV
1	1.72	1.90	1.66
2	1.46	1.81	1.35
3	1.49	1.79	1.40
4	1.48	1.71	1.41
5	1.72	2.13	1.60
6	1.19	1.32	1.15
7	1.37	1.44	1.34
8	1.78	2.19	1.65
9	1.31	1.51	1.25
10	1.74	2.19	1.59
11	1.64	1.88	1.57
12	1.55	1.81	1.47
13	1.28	1.64	1.17
14	1.27	1.33	1.25
15	1.84	2.22	1.72
16	1.87	2.38	1.71
17	1.53	1.79	1.44
18	1.16	1.36	1.10
19	1.66	2.26	1.47
20	1.90	2.50	1.71
Total	1.55	1.86	1.45

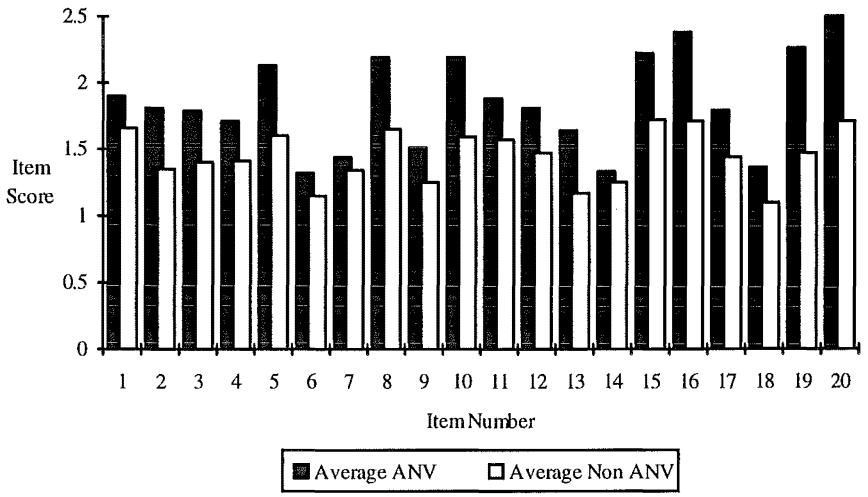

Figure 8. *STAI-State Anxiety Individual Item Averages*

C) State Anxiety mm Scores

Where state anxiety was measured using a 10cm visual analogue scale, the patients who developed ANV rated their anxiety greater than those who did not go on to develop ANV although this difference was not statistically significant ($t(23)=1.9204$, ns). The average score, as measured in millimetres, were 26 (SD:21.27) for the ANV group and 14 (SD:16.02) for those in the non-ANV group - 86% higher in the ANV group. Table 17 shows that the average state anxiety mm scores were higher for those in the ANV group in five out of the six cycles available to compare, with only cycle one being significantly different. The ANV group scored 1.14 standard deviations higher at cycle one ($t(21)=2.6429$, $P<0.05$), 0.81 SDs higher at cycle two ($t(23)=1.5937$, ns), 0.62 SDs higher at cycle three ($t(23)=1.2782$, ns), 0.93 SDs higher at cycle four ($t(22)=2.0728$, ns), 0.27 SDs higher at cycle five ($t(9)=0.5284$, ns), but 0.28 SDs lower than the non-ANV group at cycle six ($t(8)=-0.5300$, ns). The highest scores recorded by ANV patients were 92% higher than the highest state anxiety mm scores recorded by non-ANV patient on average ($t(23)=2.9809$, $P<0.01$). On the other hand, the lowest scores on average were from the patients in the non-ANV group, 61% lower than those in the ANV group, although this was not significant ($t(23)=1.4777$, ns).

The regression lines in Figure 9 show a very strong downward trend in the state anxiety mm scores for the ANV group (slope=-6.50, r=-0.96). Although the non-ANV group has an upward trend overall (slope=1.68), there is a downward trend for the first

six cycles (slope=-2.22). Cycles seven and eight include only two and one observations respectively, so the sharp increase in state mm scores for these cycles is probably just a result of this reduction in patient numbers.

Table 17.
State Anxiety 10cm Visual Analogue Scale Averages

	All Patients	ANV	Non-ANV
Cycle 1	24.28	41.13 (n=6)	20.74 (n=19)
Cycle 2	18.92	29.92 (n=6)	15.45 (n=19)
Cycle 3	16.86	25.25 (n=6)	14.21 (n=19)
Cycle 4	14.46	27.00 (n=6)	10.28 (n=18)
Cycle 5	11.36	14.50 (n=4)	9.57 (n=7)
Cycle 6	7.50	4.50 (n=4)	9.50 (n=6)
Cycle 7	29.50	*	29.50 (n=2)
Cycle 8	33.00	*	33.00 (n=1)
Average	17.11	26.30	14.21
S.D.	17.95	21.27	16.02
Highest	32.10	50.58	26.26
Lowest	7.00	13.00	5.11

*no patients who developed ANV were followed for more than six cycles.

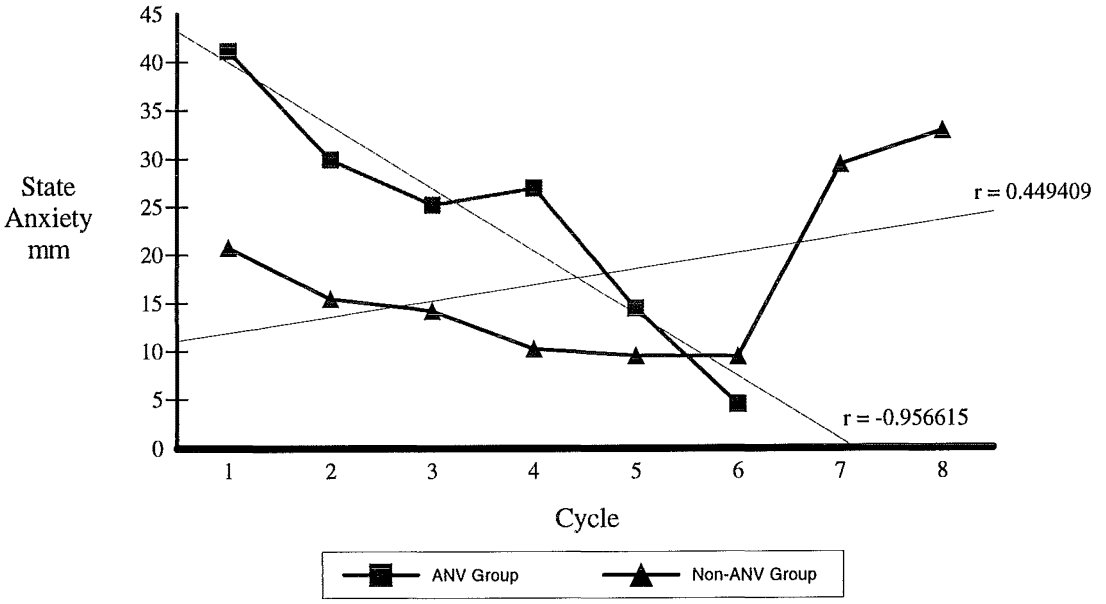

Figure 9. *State Anxiety Visual Analogue Scale Averages*

TRAIT ANXIETY

A) STAI-T Scores

The two groups also scored differently on the twenty items in the STAI-Trait subscale. The average score for those who developed ANV was 37 (SD:9.05), 23% higher than the average recorded by those who did not develop ANV of 30 (SD:7.96; $t(23)=2.1344$, $P<0.05$). Table 18 shows that the ANV group scored significantly higher on the first three cycles; scoring 1.05 standard deviations higher at cycle one ($t(23)=2.1371$, $P<0.05$), 1.34 SDs higher at cycle two ($t(23)=3.1473$, $P<0.01$) and 1.00 SDs higher at cycle three ($t(23)=2.2522$, $P<0.05$). However, there was not a significant difference between the ANV patients and non-ANV patients for the last three cycles; only 0.63 SDs higher at cycle four ($t(22)=1.4072$, ns), 0.50 SDs higher at cycle five ($t(9)=2.1190$, ns) and 0.52 SDs higher at cycle six ($t(8)=1.4663$, ns). On average, the highest scores of the patients in the ANV group were 37% higher than those in the non-ANV group ($t(23)=2.9318$, $P<0.01$), and the lowest scores of the patients in the non-ANV group were 15% lower than those in the ANV group ($t(23)=1.3464$, ns). So, the highest scores of the ANV group were significantly higher than the highest scores of the non-ANV group, but the lowest scores of the two groups were not significantly different.

Figure 10 shows that there was a downward trend in the STAI-T scores for both groups (ANV: slope=-3.01, non-ANV: slope=-0.64) and that these downward sloping regression lines are an accurate description of the relationship between the STAI-T scores and the cycle number (ANV: r=-0.94, non-ANV: r=-0.96). So, there was a tendency for the patients to report less trait anxiety as their chemotherapy progressed.

Age was shown to have a fairly strong correlation with STAI-T scores (r=-0.56), with younger patients recording higher scores. Overall, there was a strong positive correlation between the STAI-T scores and the BDI scores (r=0.60), although this was not as strong in the ANV patients. This correlation shows that, generally, higher levels of trait anxiety were associated with higher levels of depression. There was a reasonable correlation between the STAI-T scores and the trait anxiety mm scores (r=0.49), with a stronger correlation in the ANV group (r=0.69), showing that the visual analogue scale for trait

anxiety provided good validation of the STAI-T scores. STAI-T scores were also highly correlated with posttreatment nausea severity (r=0.72) and frequency (r=0.70), but not very strong for posttreatment vomiting severity and frequency. This demonstrates that high trait anxiety was associated with more severe and frequent posttreatment nausea but not vomiting. There were good positive relationships between STAI-T scores and anticipatory nausea severity (r=0.69) and frequency (r=0.44) in the ANV group, showing that high trait anxiety was associated with more severe and frequent anticipatory nausea.

STAI-Trait scores at cycle one were correlated with anticipatory nausea severity before cycles three (r=0.62) and four (r=0.61), so that patients with high state anxiety scores at cycle one experiencing higher levels of anticipatory nausea at before cycles three and four. There was no strong relationship between cycle two STAI-T scores and consequent anticipatory nausea severity, but there was a strong positive relationship between STAI-T scores at cycle three and anticipatory nausea severity at cycle four (r=0.71). This means that the patients who recorded higher levels of trait anxiety at cycle three also experienced higher levels of anticipatory nausea at cycle four.

In comparison to the norms for the STAI-T reported by Knight, Waal-Manning and Spears(1983) of 33.11 (S.D:7.80) for the males and 36.85 (S.D:8.89) for the females, the males in this study had an average score of 32.35 (SD:8.67) and the females had an average score of 30.52 (SD:9.20).

Table 18.
State-Trait Anxiety Inventory - Trait Anxiety Averages

	All Patients	ANV	Non-ANV
Cycle 1	33.82	40.92 (n=6)	31.58 (n=19)
Cycle 2	32.70	41.75 (n=6)	29.84 (n=19)
Cycle 3	32.28	39.00 (n=6)	30.16 (n=19)
Cycle 4	30.75	34.92 (n=6)	29.36 (n=18)
Cycle 5	25.73	28.25 (n=4)	24.29 (n=7)
Cycle 6	26.00	28.75 (n=4)	24.17 (n=6)
Cycle 7	22.50	*	22.50 (n=2)
Cycle 8	21.00	*	21.00 (n=1)
Average	31.54	37.32	29.72
S.D.	8.87	9.05	7.96
Highest	36.56	45.92	33.61
Lowest	27.82	31.50	26.66

*no patients who developed ANV were followed for more than six cycles.

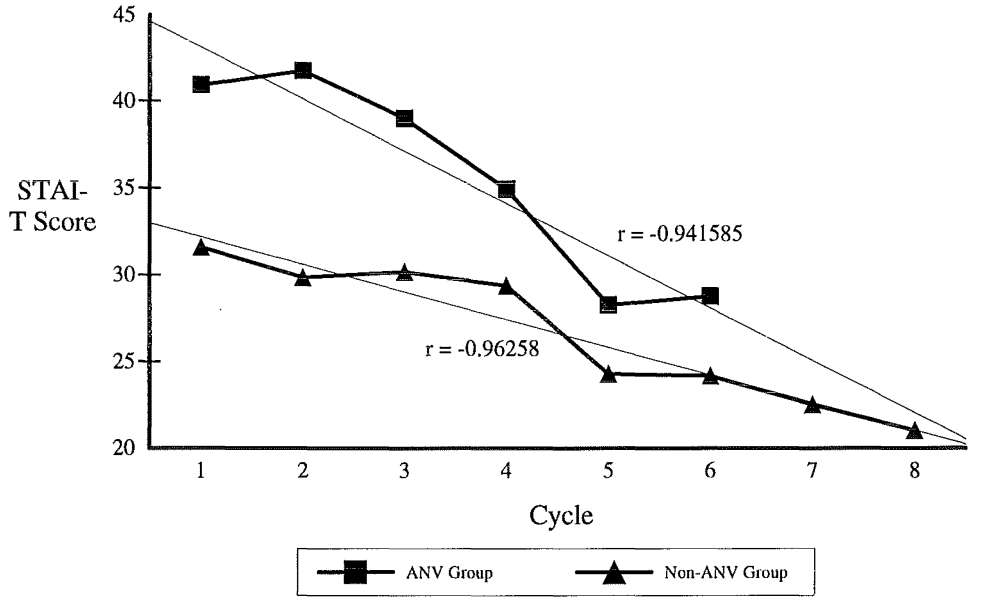

Figure 10. *STAI-Trait Anxiety Score Averages*

B) STAI-T Profiles

The ANV group, on average, scored significantly higher on six of the twenty STAI-T items. As Table 19 and Figure 11 show, the items on which the patients who developed ANV scored significantly higher were items 27 (Calm, cool, and collected; $t(23)=3.8279$, $P<0.01$), 28 (Difficulties piling up; $t(23)=2.2410$, $P<0.05$), 30 (Happy; $t(23)=2.1870$, $P<0.05$), 33 (Secure; $t(23)=2.8374$, $P<0.01$), 38 (Take disappointments keenly and can not forget them; $t(23)=2.2467$, $P<0.05$), and 39 (Steady; $t(23)=4.0571$, $P<0.01$). The items on which there was not a significant difference were items 21 (Feel pleasant), 22 (Nervous and restless), 23 (Satisfied with self), 24 (Wish could be as happy as others seem), 25 (Feel like failure), 26 (Rested), 29 (Worry over unimportant matters), 31 (Disturbing thoughts), 32 (Lack self-confidence), 34 (Make decisions easily), 35 (Feel inadequate), 36 (Content), 37 (Bothered by unimportant things), and 40 (Tension and turmoil as think over recent concerns and interests). The patients who developed ANV on average saw themselves as being less 'cool, calm, and collected', more susceptible to having difficulties piling up which they are unable to overcome, less

happy, less secure, more likely to take disappointments so keenly that they are unable to put them out of their minds, and less steady than the patients who did not develop ANV.

Table 19.
State-Trait Anxiety Inventory - Trait Anxiety Individual Item Averages

Item	Average All Pats	Average ANV	Average Non ANV
21	1.75	1.89	1.70
22	1.59	1.68	1.56
23	1.68	2.03	1.58
24	1.77	1.79	1.76
25	1.28	1.47	1.22
26	1.85	2.21	1.74
27	1.84	2.69	1.57
28	1.36	1.65	1.27
29	1.64	1.85	1.58
30	1.50	1.88	1.38
31	1.36	1.50	1.31
32	1.62	1.88	1.54
33	1.44	1.92	1.28
34	1.78	2.10	1.68
35	1.43	1.57	1.39
36	1.51	1.92	1.38
37	1.57	1.63	1.55
38	1.40	1.75	1.29
39	1.50	2.22	1.28
40	1.46	1.68	1.39
Total	1.57	1.86	1.47

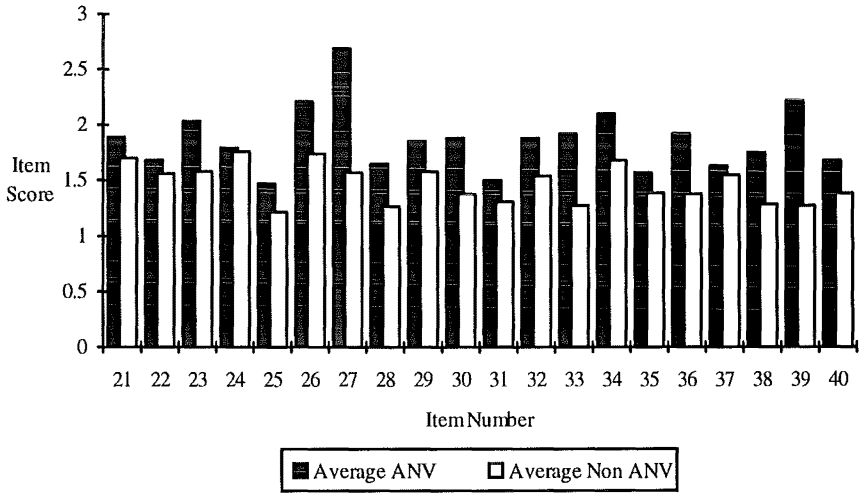

Figure 11. *STAI-Trait Anxiety Individual Item Averages*

C) Trait Anxiety mm Scores

Self-reported trait anxiety as measured by the 10cm visual analogue scale also revealed differences between those who developed ANV and those who did not. The average trait anxiety mm score was higher in the group who developed ANV than in the group who did not develop ANV, although this difference was not statistically significant ($t(23)=1.8758$, ns).

The average trait anxiety mm score among those patients who developed ANV was 27 (SD:21.43), 93% higher than the average score of 14 (SD:16.43) among those who did not develop ANV. Table 20 shows that the ANV group scored higher on average in each of the cycles comparable, but only demonstrated significant differences on cycles three and four; 1.01 SDs higher at cycle three ($t(23)=2.8606$, $P<0.01$) and 0.82 SDs higher at cycle four ($t(22)=3.3037$, $P<0.01$), but only 0.91 standard deviations higher at cycle one ($t(21)=1.2412$, ns), 0.91 SDs higher at cycle two ($t(23)=1.6804$, ns), 0.26 SDs higher at cycle five ($t(9)=0.7400$, ns), and 0.34 SDs higher at cycle six ($t(8)=0.8601$, ns). The highest scores of those in the ANV group were 53% higher than those of patients in the non-ANV group, although this was not a statistically significant difference ($t(23)=1.2715$); whereas the lowest scores of the patients in the non-ANV group were 71% lower than those in the ANV group, which was a significant difference ($t(23)=2.5388$, $P<0.05$). So, the ANV group did not have high scores significantly higher than the non-ANV group, but the non-ANV group had low scores significantly lower than the ANV group.

The linear regression lines in Figure 12 show that there was a downward trend in the trait anxiety mm scores for both groups (ANV: slope=-5.40, non-ANV: slope=-1.78) and that these lines are accurate representations of the relationship between the state anxiety mm scores and the cycle number (ANV: r=-0.97, non-ANV: r=-0.75). So, this also indicates that there was a tendency to report less trait anxiety as the patient's chemotherapy progressed.

Table 20.
Trait Anxiety 10cm Visual Analogue Scale Averages

	All Patients	ANV	Non-ANV
Cycle 1	26.33	40.38 (n=6)	23.37 (n=19)
Cycle 2	22.66	35.50 (n=6)	18.61 (n=19)
Cycle 3	14.98	29.25 (n=6)	10.47 (n=19)
Cycle 4	10.50	21.92 (n=6)	6.69 (n=18)
Cycle 5	11.91	15.00 (n=4)	10.14 (n=7)
Cycle 6	12.55	16.38 (n=4)	10.00 (n=6)
Cycle 7	7.00	*	7.00 (n=2)
Cycle 8	10.00	*	10.00 (n=1)
Average	17.39	27.19	14.30
S.D.	18.65	21.43	16.43
Highest	30.80	41.83	27.32
Lowest	7.08	15.25	4.50

*no patients who developed ANV were followed for more than six cycles.

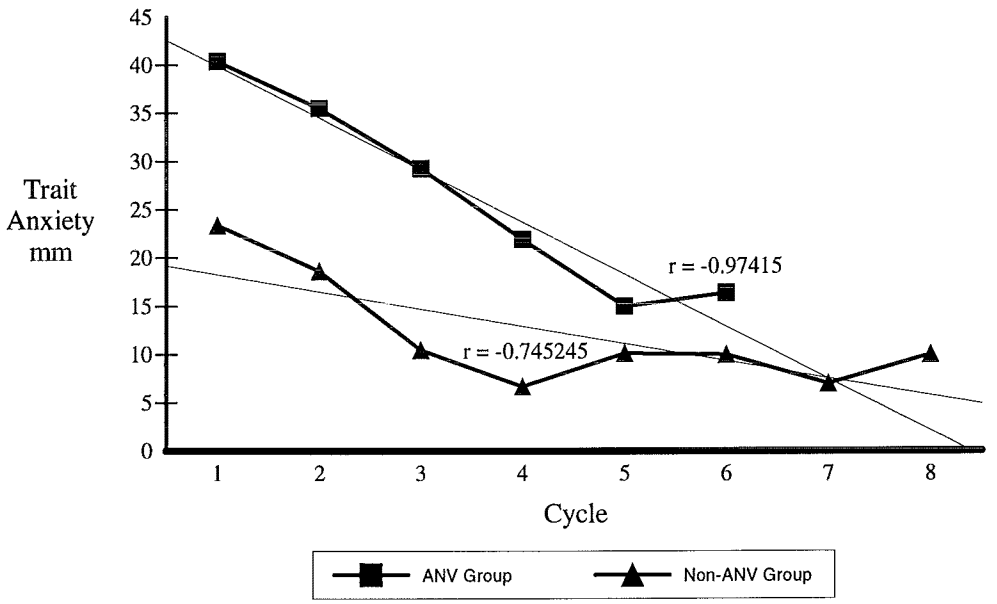

Figure 12. *Trait Anxiety Visual Analogue Scale Averages*

DEPRESSION

A) BDI Total Scores

The severity of depression recorded by the Beck Depression Inventory revealed similar differences between the ANV and non-ANV groups as were demonstrated by the state anxiety and trait anxiety measures. On average, the ANV group scored

significantly higher than the non-ANV group ($t(23)=2.3155$, $P<0.05$), with the ANV group having an average score of 10 (SD:5.53), 67% higher than the average score of 6 (SD:4.63) in the non-ANV group. Table 21 shows that the ANV group scored higher on all six cycles compared, although the difference was significant only on the first three cycles. The ANV group scored 1.10 standard deviations higher at cycle one ($t(23)=3.5975$, $P<0.01$), 1.12 SDs higher at cycle two ($t(23)=2.8360$, $P<0.01$) and 0.99 SDs higher at cycle three ($t(23)=2.2424$, $P<0.05$). There was not a significant difference between the two groups for the last three cycles; being only 0.60 SDs higher at cycle four ($t(22)=1.0217$, ns), 0.67 SDs higher at cycle five ($t(9)=1.7026$, ns) and 0.63 SDs higher at cycle six ($t(8)=1.6323$, ns). The highest scores on average were scored by the ANV group, 82% higher than those scored by the non-ANV group ($t(23)=2.5988$, $P<0.05$). The lowest scores on average were scored by the non-ANV group, 51% lower than those scored by the ANV group ($t(23)=1.8257$, ns). So, the highest scores of the ANV group were significantly higher than the highest scores of the non-ANV group, but the lowest scores of the two groups were not significantly different.

Figure 13 shows that there was tendency for patients to report less depression as their chemotherapy progressed. The downward sloping regression lines (ANV: slope=-0.98, non-ANV: slope=-0.64) are an accurate representation of the relationship between the BDI total scores and the cycle number (ANV: r=-0.96, non-ANV: r=-0.87).

The BDI-Total scores were highly correlated with the depression mm scores (r=0.70), showing that the visual analogue scale for depression provided good validation for the BDI. There were also good overall correlations between the BDI-Total scores and posttreatment nausea (r=0.55) and vomiting (r=0.65) severity, although the ANV group demonstrated a relatively strong negative correlation between the BDI-Total scores and posttreatment nausea severity (r=-0.48). This means that overall there was a tendency for the patients with the higher BDI scores to experience more severe posttreatment nausea and vomiting, but in the ANV group there was a tendency for the patients with the lower BDI scores to experience more severe posttreatment nausea. There was also an opposite correlation between the BDI-Total scores and posttreatment nausea frequency (ANV r=-0.73, Non-ANV r=0.55), showing that lower BDI scores in the ANV group

were associated with more frequent posttreatment nausea whereas higher BDI scores in the non-ANV group were associated with more frequent posttreatment nausea. There were consistently high correlations between the BDI-Total scores and posttreatment vomiting frequency (r=0.64 overall), showing that higher BDI scores were associated with more frequent posttreatment vomiting in both groups. There was a very strong correlation between the BDI-Total scores and SEEQ-Total scores in the ANV group (r=0.87) but not in the non-ANV group (r=0.24). This means that the patients in the ANV group with high BDI scores were also likely to have high SEEQ-Total scores, and that those with the high scores were expecting more side effects from their treatment than those with lower scores.

There were no strong relationships between BDI scores and consequent levels of anticipatory nausea, although most of the relatively small correlations calculated were negative, meaning there was a tendency for those who scored higher on the BDI to experience less severe anticipatory nausea.

Table 21.
Beck Depression Inventory Total Score Averages

	All Patients	ANV	Non-ANV
Cycle 1	7.50	12.42 (n=6)	6.52 (n=19)
Cycle 2	6.14	10.92 (n=6)	4.67 (n=19)
Cycle 3	6.98	11.42 (n=6)	6.10 (n=19)
Cycle 4	6.52	8.92 (n=6)	5.75 (n=18)
Cycle 5	5.55	8.25 (n=4)	4.67 (n=7)
Cycle 6	5.45	7.63 (n=4)	4.25 (n=6)
Cycle 7	3.00	*	3.00 (n=2)
Cycle 8	1.00	*	1.00 (n=1)
Average	6.45	10.06	5.54
S.D.	5.36	5.53	4.63
Highest	9.82	14.92	8.21
Lowest	3.48	5.67	2.79

*no patients who developed ANV were followed for more than six cycles.

The Center for Cognitive Therapy has distributed the following guidelines for BDI cut-off scores: none or minimal depression = <10; mild to moderate depression = 10-18; moderate to severe depression = 19-29; and severe depression = 30-63. Table 22 shows the clinical ratings for the patients in this study when these guidelines are used.

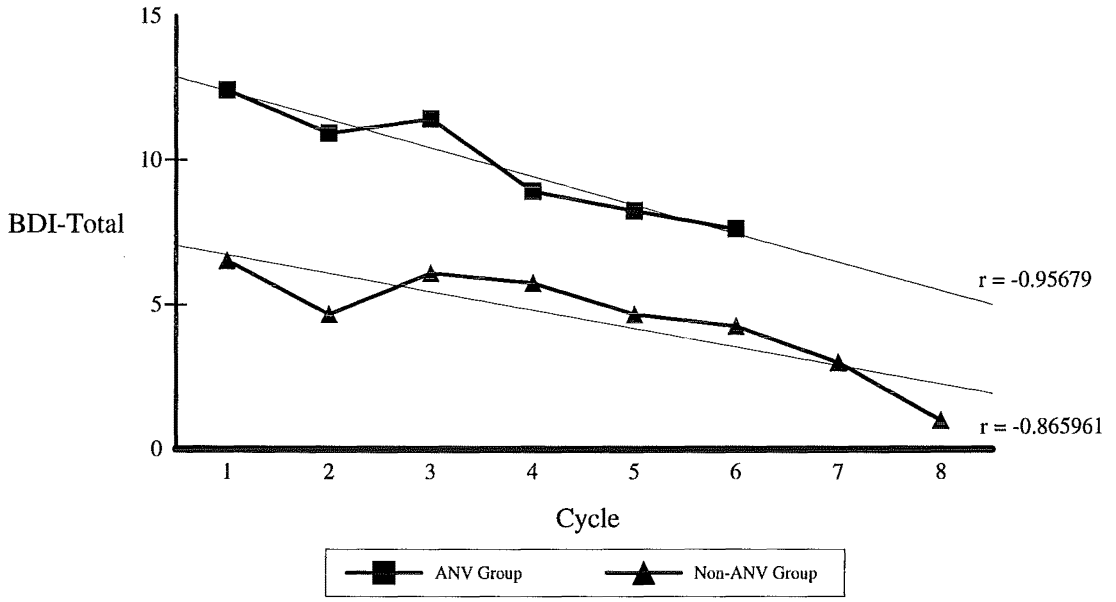

Figure 13. *Beck Depression Inventory Total Score Averages*

As can be seen in Table 22, on average the patients who developed ANV reported symptoms of depression on the BDI which equate to mild to moderate levels of depression, whereas the patients who did not develop ANV recorded none or minimal levels of depression on average. Three (50%) of the ANV patients had average BDI scores in the mild to moderate range of depression whereas only one (5%) of the non-ANV patients had an average BDI score in the mild to moderate range, with the remainder of both groups having average scores in the none to minimal range, except one non-ANV patient with an average score in the moderate to severe range. Table 22 also shows that only two of the ANV patients never had BDI scores above the none or minimal level, whereas two had scores in the mild to moderate range and two had maximum scores in the moderate to severe range.

Table 22.
Clinical Ratings for the Average BDI Scores

Patient	Average BDI Score	Clinical Rating	Most Severe (Rating)
1	16.33	Mild-Moderate	21 (Moderate-Severe)
2	5.67	None or Minimal	9 (None or Minimal)
4	12.83	Mild-Moderate	18 (Mild-Moderate)
7	7.25	None or Minimal	22 (Moderate-Severe)
14	11.75	Mild-Moderate	17 (Mild-Moderate)
18	6.50	None or Minimal	9 (None or Minimal)
3	5.17	None or Minimal	7 (None or Minimal)
5	4.33	None or Minimal	7 (None or Minimal)
6	19.25	Moderate-Severe	25 (Moderate-Severe)
8	0.00	None or Minimal	0 (None or Minimal)
9	4.00	None or Minimal	7 (None or Minimal)
10	2.25	None or Minimal	7 (None or Minimal)
11	4.00	None or Minimal	5 (None or Minimal)
13	1.60	None or Minimal	4 (None or Minimal)
15	2.50	None or Minimal	4 (None or Minimal)
16	4.14	None or Minimal	8 (None or Minimal)
17	7.67	None or Minimal	12 (Mild-Moderate)
19	5.00	None or Minimal	8 (None or Minimal)
20	2.63	None or Minimal	3 (None or Minimal)
21	4.25	None or Minimal	6 (None or Minimal)
22	4.25	None or Minimal	11 (Mild-Moderate)
23	8.88	None or Minimal	12 (Mild-Moderate)
24	8.25	None or Minimal	15 (Mild-Moderate)
25	1.25	None or Minimal	2 (None or Minimal)
26	11.50	Mild-Moderate	13 (Mild-Moderate)
All Patients	6.45	None or Minimal	10.08 (Mild-Moderate)
ANV	10.06	Mild-Moderate	16.00 (Mild-Moderate)
Non-ANV	5.54	None or Minimal	8.21 (None or Minimal)

B) BDI Physiological Subscale and Cognitive/Affective Subscale Scores

When the Beck Depression Inventory scores were divided into the physiological subscale (items 14-21) and the cognitive/affective subscale (items 1-13) the differences between the two groups were evident more in the affective/cognitive subscale than in the physiological subscale. The two subscales of the BDI were very highly correlated (r=0.93), so that a patient who scored high on the physiological symptoms also tended to score high on the affective/cognitive symptoms and vice versa.

The average BDI-PS score for the ANV group was higher than for the patients in the non-ANV group but this difference did not reach a significant level (t(23)=1.5745, ns). The average BDI-PS score for the ANV group was 6 (SD:4.12), 50% higher than the average for the non-ANV group of 4 (SD:3.15). As Table 23 shows, the difference was

recorded over all of the six cycles compared and was found to be statistically significant on the first two cycles; with the ANV group scoring 0.79 standard deviations higher at cycle one ($t(23)=2.2008$, $P<0.05$), 0.95 SDs higher at cycle two ($t(23)=2.2091$, $P<0.05$), but only 0.87 SDs higher at cycle three ($t(23)=1.6519$, ns), 0.47 SDs higher at cycle four ($t(22)=0.8038$, ns), 0.59 SDs higher at cycle five ($t(9)=1.1268$, ns), and 0.45 SDs higher at cycle six ($t(8)=0.8785$, ns). The highest BDI-PS scores on average were recorded by the ANV group, 61% higher than those of the non-ANV group ($t(23)=1.8930$, ns); whereas the lowest BDI-PS scores were recorded by the non-ANV group, 46% lower than those of the ANV group ($t(23)=1.3960$, ns). So, the ANV and non-ANV groups did not score significantly higher or lower than each other on the physiological subscale of the BDI.

The regression lines in Figure 14 show that there was a downward trend in the scores for the BDI physiological subscale in both groups (ANV: slope=-0.51, non-ANV: slope=-0.37). These lines are an accurate representation of the relationship between the BDI-PS scores and the cycle number (ANV: r=-0.92, non-ANV: r=-0.88).

Table 23.
Beck Depression Inventory Physiological Subscale Averages

	All Patients	ANV	Non-ANV
Cycle 1	4.66	6.83 (n=6)	3.97 (n=19)
Cycle 2	4.22	6.83 (n=6)	3.39 (n=19)
Cycle 3	4.62	7.00 (n=6)	3.87 (n=19)
Cycle 4	4.31	5.58 (n=6)	3.89 (n=18)
Cycle 5	3.64	5.00 (n=4)	2.86 (n=7)
Cycle 6	3.65	4.63 (n=4)	3.00 (n=6)
Cycle 7	2.00	*	2.00 (n=2)
Cycle 8	1.00	*	1.00 (n=1)
Average	4.24	5.99	3.69
S.D.	3.61	4.12	3.15
Highest	6.42	9.00	5.61
Lowest	2.18	3.33	1.82

*no patients who developed ANV were followed for more than six cycles.

The patients in the ANV group recorded BDI-C/AS scores significantly higher than those who did not develop ANV ($t(23)=3.0386$, $P<0.01$). The average BDI-C/AS score in the ANV group was 4 (SD:3.22), twice as high as the average score of 2 (SD:2.01) in

the non-ANV group. Table 24 shows that the ANV group scored consistently higher than the non-ANV group, with significant differences on the first three cycles. The ANV group scored 1.34 standard deviations higher at cycle one ($t(23)=3.1647$, $P<0.01$), 1.05 SDs higher at cycle two ($t(23)=2.6458$, $P<0.05$) and 1.00 SDs higher at cycle three ($t(23)=2.3953$, $P<0.05$), but only 0.56 SDs higher at cycle four ($t(22)=1.2033$, ns), 1.43 SDs higher at cycle five ($t(9)=2.1932$, ns) and 1.34 SDs higher at cycle six ($t(8)=2.2094$, ns). On average, the highest scores recorded by the ANV group were 190% higher than those recorded by the non-ANV group ($t(23)=3.9888$, $P<0.01$); whereas the lowest scores recorded by the non-ANV group were 60% lower than those of the ANV group ($t(23)=1.6606$, ns). So the highest scores recorded by the ANV group were significantly higher than those recorded by the non-ANV group, but there was no significant difference between the lowest scores recorded by the two groups.

The regression lines in Figure 15 show that both group maintained relatively stable BDI affective/cognitive subscale scores (ANV: slope=-0.09, non-ANV: slope=-0.21). The scores for the non-ANV group were very stable (r=-0.83) but the scores for the non-ANV group were relatively erratic (r=-0.22).

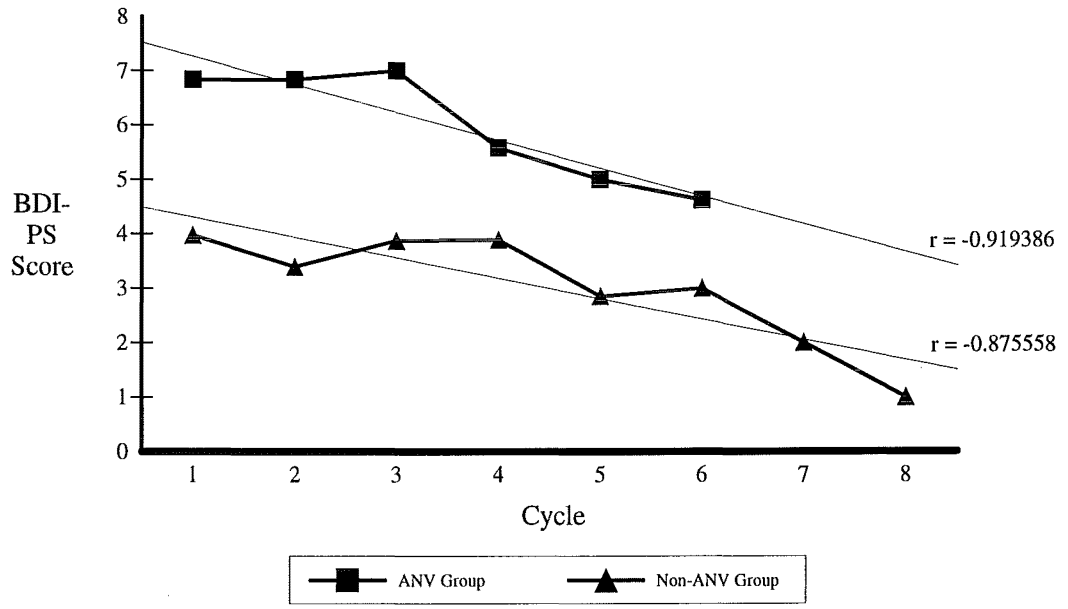

Figure 14. *Beck Depression Inventory Physiological Subscale Averages*

Table 24.
Beck Depression Inventory Affective/Cognitive Subscale Averages

	All Patients	ANV	Non-ANV
Cycle 1	2.84	5.58 (n=6)	1.97 (n=19)
Cycle 2	1.92	4.08 (n=6)	1.24 (n=19)
Cycle 3	2.36	4.42 (n=6)	1.71 (n=19)
Cycle 4	2.21	3.33 (n=6)	1.83 (n=18)
Cycle 5	2.55	5.00 (n=4)	1.14 (n=7)
Cycle 6	2.45	4.63 (n=4)	1.00 (n=6)
Cycle 7	1.00	*	1.00 (n=2)
Cycle 8	0.00	*	0.00 (n=1)
Average	2.30	4.44	1.62
S.D.	2.70	3.22	2.01
Highest	4.22	8.42	2.89
Lowest	1.06	2.00	0.76

*no patients who developed ANV were followed for more than six cycles.

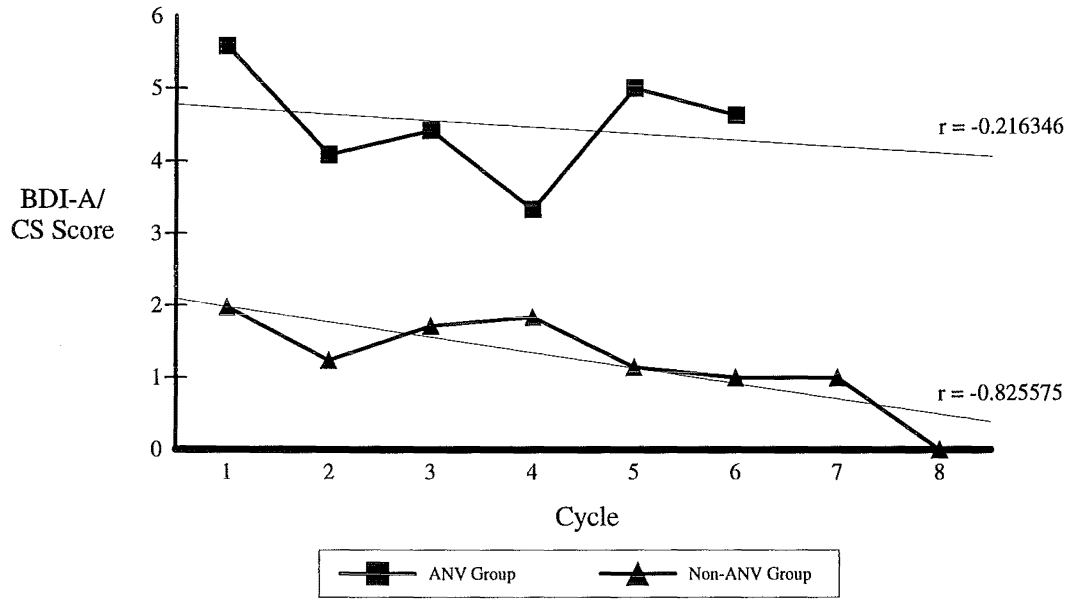

Figure 15. *Beck Depression Inventory Affective/Cognitive Subscale Averages*

C) BDI Profiles

Although the ANV group scored higher on the BDI, they did not score significantly higher on all of the items of the BDI. Table 25 and Figure 16 show that the patients who developed ANV only scored significantly higher on items 2 (Pessimism; $t(23)=3.1653$, $P<0.01$), 4 (Lack of satisfaction; $t(23)=2.1618$, $P<0.05$), 18 (Loss of Appetite; $t(23)=2.6316$, $P<0.05$) and 21 (Loss of Libido; $t(23)=2.0937$, $P<0.05$); but there was no

significant difference between the two groups on items 1 (Mood), 3 (Sense of failure), 5 (Guilt Feelings), 6 (Sense of punishment), 7 (Self-dislike), 8 (Self-accusation), 9 (Suicidal Wishes), 10 (Crying), 11 (Irritability), 12 (Social withdrawal), 13 (Indecisiveness), 14 (Distortion of Body Image), 15 (Work Inhibition), 16 (Sleep Disturbance), 17 (Fatigability), 19 (Weight Loss) and 20 (Somatic Preoccupation). The patients who developed ANV were significantly more pessimistic, less satisfied, lost more weight, and experienced a larger decline in their libido.

Table 25.
Beck Depression Inventory Individual Item Averages

Item Number	Average All Pats	Average ANV	Average Non ANV
1	0.19	0.29	0.15
2	0.13	0.38	0.05
3	0.08	0.17	0.05
4	0.29	0.57	0.20
5	0.07	0.10	0.07
6	0.21	0.49	0.13
7	0.09	0.14	0.07
8	0.18	0.36	0.13
9	0.03	0.00	0.04
10	0.12	0.24	0.08
11	0.49	0.78	0.39
12	0.16	0.32	0.10
13	0.15	0.26	0.11
14	0.18	0.24	0.16
15	0.74	1.00	0.66
16	0.58	0.74	0.54
17	0.96	1.08	0.92
18	0.35	0.75	0.22
19	0.47	0.81	0.37
20	0.57	0.72	0.52
21	0.36	0.69	0.25
Total	0.30	0.48	0.25

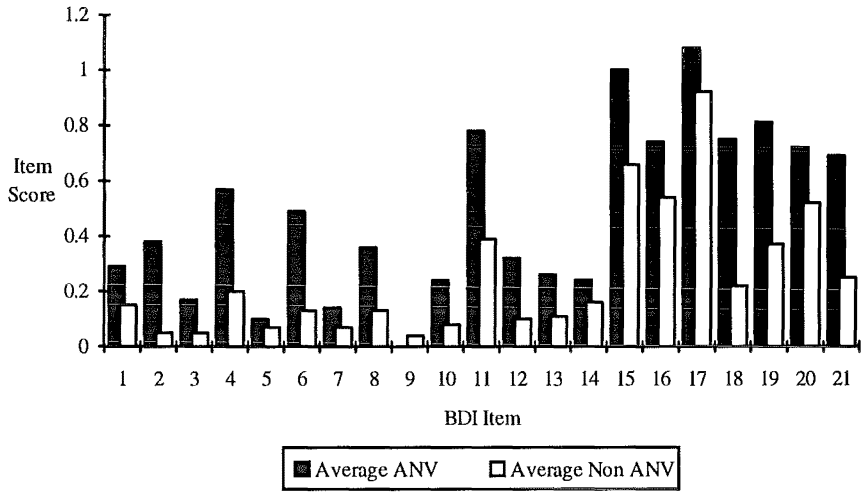

Figure 16. *BDI Individual Item Averages*

D) Depression mm Scores

The levels of depression reported by the patients in the ANV group, when measured using the 10cm visual analogue scale, were significantly higher than the levels of depression reported by those in the non-ANV group ($t(23)=2.3416$, $P<0.05$). The average depression mm score for the ANV group was 17 (SD:17.46), 113% higher than the average of 8 (SD:9.50) for the non-ANV group. Table 26 shows that the ANV group scored higher on average at five out of the six cycles compared, with significantly higher average scores on the second and third cycles. The ANV group scored 1.43 SDs higher at cycle two ($t(23)=3.0008$, $P<0.01$) and 1.62 SDs higher at cycle three ($t(23)=3.0556$, $P<0.01$), but only 0.75 standard deviations higher at cycle one ($t(21)=1.6738$, ns), 0.34 SDs higher at cycle four ($t(22)=1.0512$, ns), 0.21 SDs lower at cycle five ($t(9)=-0.9941$, ns) and 0.52 SDs higher at cycle six ($t(8)=0.6991$, ns). The highest scores on average were recorded by those in the ANV group, 120% higher than those of the non-ANV group ($t(23)=2.7019$, $P<0.05$). The lowest scores on average were recorded by the non-ANV group, 61% lower than those of the ANV group ($t(23)=1.2192$, ns). So, the highest scores recorded by the ANV group were significantly higher than the highest scores recorded by the non-ANV group, but the two groups did not have significantly different low scores.

Figure 17 shows that the depression mm scores for the non-ANV group were relatively stable over time (slope=-0.37) but the scores for the ANV group were quite varied and not well represented by a straight line.

Table 26.
Depression 10cm Visual Analogue Scale Averages

	All Patients	ANV	Non-ANV
Cycle 1	8.70	16.63 (n=6)	7.03 (n=19)
Cycle 2	11.96	25.83 (n=6)	7.58 (n=19)
Cycle 3	13.98	29.67 (n=6)	9.03 (n=19)
Cycle 4	8.40	11.67 (n=6)	7.31 (n=18)
Cycle 5	4.32	2.63 (n=4)	5.29 (n=7)
Cycle 6	8.50	12.50 (n=4)	5.83 (n=6)
Cycle 7	13.50	*	13.50 (n=2)
Cycle 8	0.00	*	0.00 (n=1)
Average	9.89	17.21	7.58
S.D.	12.76	17.46	9.50
Highest	19.88	33.92	15.45
Lowest	2.22	4.08	1.63

*no patients who developed ANV were followed for more than six cycles.

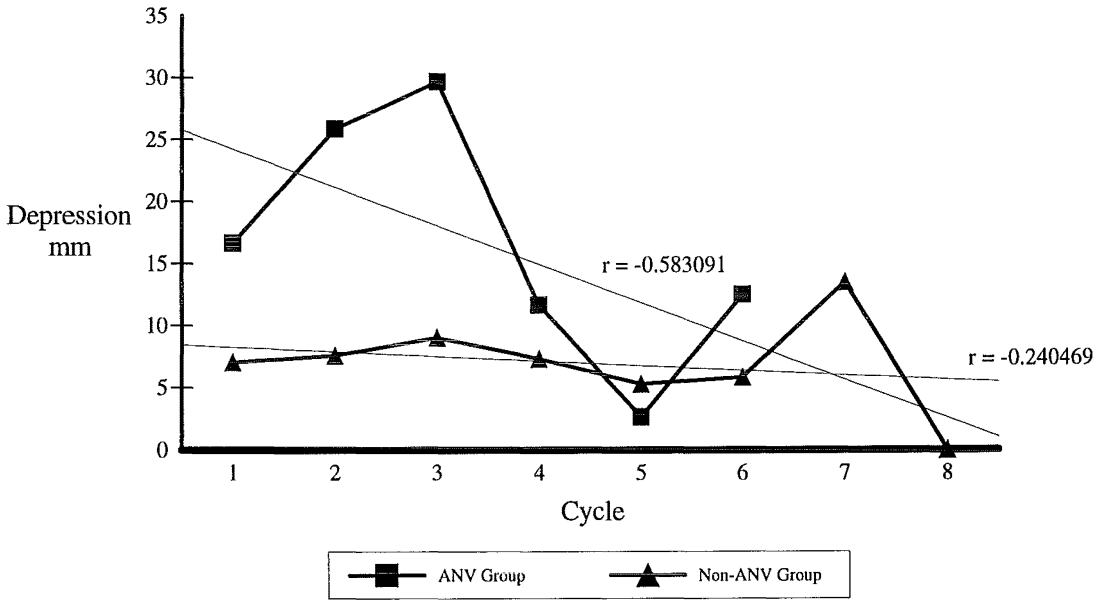

Figure 17. *Depression Visual Analogue Scale Averages*

PATIENT EXPECTATIONS

A) SEEQ Totals

Table 27 and Figure 18 show that those patients who developed ANV did not expect to experience significantly more side effects from their chemotherapy than those who did not develop ANV (t(20)=1.6139, ns).

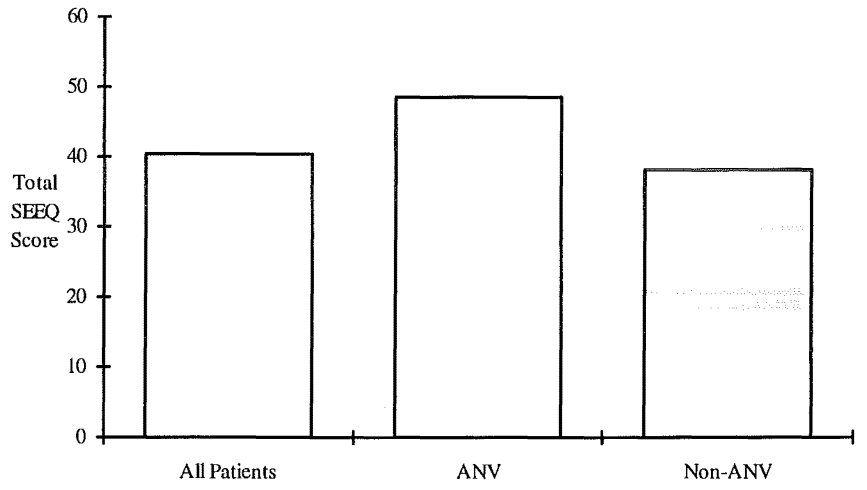

Figure 18. *Average Total Scores on the Side Effect Expectancy Questionnaire*

B) Nausea and Vomiting Expectancy

Table 27 and Figure 19 show that the patients who developed ANV generally started their chemotherapy expecting to experience nausea and vomiting as a side effect of their treatment and that the patients who did not develop ANV generally did not expect to nausea and vomiting to be a side effect of their treatment (Nausea:t(20)=2.5424, $P<0.05$; Vomiting:t(20)=2.5885, $P<0.05$). The results of the SEEQ also show that patients usually expected to experience nausea more than they expected vomiting as a side effect of their chemotherapy.

Table 27.
Side Effect Expectancy Questionnaire Results

Patient	Total	Nausea	Vomiting	Rated >3
1	60	4	4	Tiredness, Hairloss, Change in taste/appetite, Nausea, Vomiting, Nervousness, Weakness, Problems with sex, Constipation
2	*	*	*	*
3	36	3	4	Tiredness, Hairloss, Nervousness, Vomiting, Skin itching
4	47	4	4	Weight loss, Nausea, Vomiting, Tiredness, Hair loss, Change in taste/appetite, Sleep problems, Chills
5	59	3	3	Tiredness, Hairloss, Nervousness, Weakness, Diarrhoea, Chills
6	40	3	3	Sleep problems
7	47	5	4	Nausea, Tiredness, Weakness, Vomiting, Chills
8	36	3	3	None
9	41	1	1	Nervousness
10	44	4	2	Nausea, Tiredness, Weakness
11	24	2	2	None
12	35	4	4	Nausea, Vomiting, Change in taste/appetite
13	16	1	1	None
14	49	4	3	Hairloss, Nausea
15	51	3	3	Tiredness, Hairloss, Change in taste/appetite, Nervousness, Pain, Diarrhoea, Sleep problems
16	16	1	1	None
17	31	3	1	None
18	40	3	2	Tiredness
19	*	*	*	*
20	50	1	1	Hairloss, Skin itching, Nervousness, Weight loss, Sleep problems
21	46	4	3	Tiredness, Hairloss, Weakness, Nausea
22	*	*	*	*
23	55	3	3	Sleep problems, Hairloss, Nervousness, Weight loss, Pain, Weakness, Chills
24	37	2	2	Skin itching
25	19	4	1	Nausea
26	51	4	2	Tiredness, Nausea, Weakness, Diarrhoea
All	40.43 (12.71)	3.00 (1.17)	2.48 (1.12)	
ANV	48.60 (7.23)	4.00 (0.71)	3.40 (0.89)	
Non-ANV	38.17 (13.10)	2.72 (1.13)	2.22 (1.06)	

*The Side Effect Expectancy Questionnaire was not completed by these patients.

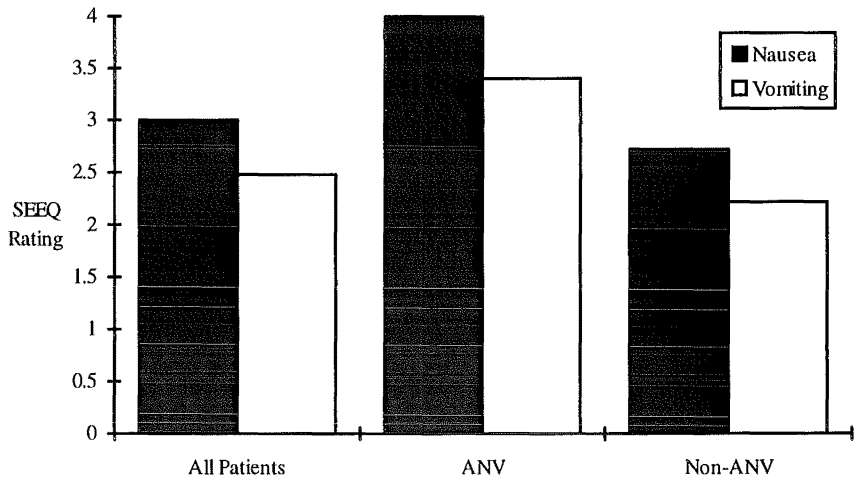

Figure 19. *Average Expectation Ratings for the Nausea and Vomiting Items*

There was a high correlation between the SEEQ-Total scores and the expected nausea frequency (maximum estimate r=0.71, mean estimate r=0.69) and severity (maximum estimate r=0.69, mean estimate r=0.68). This means that the patients with the most emetogenic chemotherapy protocols were expecting more side effects from their treatment. SEEQ-Nausea scores were reasonably well correlated with anticipatory nausea severity (r=0.46) and frequency (r=0.48), as was SEEQ-Vomiting correlated with anticipatory nausea severity (r=0.44) and frequency (r=0.49). This shows that the patients who were expecting nausea as a side effect of their treatment were also the patients who experienced more severe and frequent anticipatory nausea.

Chapter IV

DISCUSSION

The primary aims of this study were to assess the prevalence of anticipatory nausea and vomiting in cancer patients who are receiving their chemotherapy in a setting where the new 5-HT_3 receptor antagonists are being used for antiemetic therapy, and to identify any relationships that may exist between the development of anticipatory symptoms and various demographic, clinical and psychological variables.

Summary of Results

This study has produced a number of interesting results. The prevalence of anticipatory nausea and vomiting in this study is similar to the prevalence rate reported in studies where less effective antiemetics have been used.

The patients who developed ANV reported higher levels of state anxiety, trait anxiety and depression than the patients who did not develop ANV. The difference in anxiety and depression was more evident prior to the first few chemotherapy cycles. The anticipatory patients were expecting nausea and vomiting as a side effect of their chemotherapy more than the patients who did not develop ANV.

The ANV patients were younger than the non-ANV patients; tending to be under forty years of age. The anticipatory patients were receiving more emetogenic chemotherapy protocols and experienced more frequent and severe posttreatment nausea and vomiting than those who did not develop ANV.

The Prevalence of ANV and the Introduction of 5-HT_3 Receptor Antagonists

If the introduction of 5-HT_3 receptor antagonists has decreased chemotherapy-induced nausea and vomiting, and the classical conditioning model of acquisition is correct, then there should be a decreased incidence of anticipatory nausea and vomiting in an environment where 5-HT_3 receptor antagonists are provided for patients who are likely to experience nausea and vomiting as a side effect of their treatment. The patients in this study did receive 5-HT_3 receptor antagonists if they were expected to experience nausea and vomiting with their chemotherapy, so it follows that the prevalence of ANV

in this study should be less than the 20-40% prevalence rate reported in studies where 5-HT_3 receptor antagonists have not been available (Bernstein, 1991).

Contrary to this hypothesis, the prevalence rate of ANV for the patients in this study was 24% - within the range reported for populations where 5-HT_3 receptor antagonists have not been used. In fact, all of the patients who developed ANV were given 5-HT_3 receptor antagonists for their nausea and vomiting. Also, there were two patients who were not recorded as having anticipatory nausea but who had experienced an anticipatory loss of appetite and a general feeling of anxiousness a day or two before receiving their chemotherapy, perhaps indicating that they may have been close to developing ANV.

There are a number of possible explanations for the unexpectedly high prevalence rate in this study. If the group of patients in this study included an unusually large proportion of highly emetogenic protocols then the high prevalence of ANV could have been attributed to the biased sample. The protocols used in this study were predominantly in the moderate to severe range for their emetogenicity, suggesting that this may have some influence on the prevalence of ANV in this sample of patients. The prevalence rate of ANV in this study was remarkably similar to the prevalence rate of 23% reported by Watson et al. (1992), which also contained a large percentage of patients receiving moderate to severely emetic chemotherapy regimens. The only discernible difference between the current study and the Watson et al. (1992) study is the use of 5-HT_3 receptor antagonists as the main antiemetics. Therefore, it would seem that the introduction of 5-HT_3 receptor antagonists has had little effect on the incidence of ANV in patients receiving moderate to severely emetic protocols. Additionally, the prevalence of anticipatory vomiting in this study and in the Watson et al. (1992) study are both 4%.

Another explanation may be found in the small sample size. Each patient who developed ANV added 4% to the prevalence rate, whereas with a larger sample the influence of individuals on the overall prevalence rate would have been much less.

However, even with the prevalence at 24%, the severity of the anticipatory nausea and vomiting was considerably lower than in studies where 5-HT_3 antagonists have not

been used. The average level of anticipatory nausea in this study was 'very mild' whereas the average level of nausea and vomiting reported by Dunne et al. (1992) was in the 'moderate' to 'severe' range, using the same measure of nausea and vomiting (MANE) but using metoclopramide and prochlorperazine for antiemetic therapy. Also, Boakes and colleagues (1993) reported that 24% of their patients experienced 'moderate' to 'severe' anticipatory nausea. Therefore, it would appear that although the introduction of 5-HT_3 receptor antagonists may not have reduced the incidence of ANV greatly, there has been an apparent reduction in the severity of the anticipatory symptoms experienced.

The Role of Anxiety and Depression in the Development of ANV

STATE ANXIETY

The results of this study replicate one of the findings which has been consistently reported in most research on anticipatory nausea and vomiting - that higher levels of state anxiety are present in patients who develop anticipatory nausea and vomiting (Morrow & Dobkin, 1988; Andrykowski, 1990). The relationship which exists between the development of ANV and the patient's level of state anxiety has often been discussed, as to whether the ANV patients are more anxious as a result of experiencing more nausea and vomiting (both posttreatment and pretreatment) or whether these patients are more anxious right from the start of their chemotherapy. What has been demonstrated here is that the ANV patients scored significantly higher than the non-ANV patients on the STAI-State anxiety items before their first three cycles of chemotherapy but there was no significant difference prior to the fourth, fifth, and sixth cycles. On the visual analogue scale for state anxiety, the ANV patients only scored significantly higher than the non-ANV patients before their first cycle of chemotherapy. However, neither posttreatment nor pretreatment nausea and vomiting reached a peak in either group until after the third and fourth cycles of chemotherapy. Therefore, the differences in state anxiety levels were present prior to the development of the highest levels of posttreatment and pretreatment nausea and vomiting. The level of state anxiety

reported by the patients prior to their first cycle of chemotherapy was found to be highly correlated with anticipatory nausea severity before their second and third cycles. All of these findings suggest that patients who are more anxious before their first few chemotherapy cycles, and especially prior to receiving their first treatment, are more susceptible to developing anticipatory nausea and vomiting, as well as experiencing more posttreatment nausea and vomiting. More evidence for the importance of the first few treatments in the development of ANV comes from the observation that state anxiety (STAI-S and state mm) decreased over time and this was especially true for the ANV patients. This explains why the difference between the two groups decreased to an insignificant level, as the ANV patients became less anxious over time but the non-ANV patients remained relatively stable. This suggests that the ANV patients were initially very upset by the chemotherapy process but were less distressed as they became accustomed to their treatment; whereas the non-ANV patients did not react as strongly to their chemotherapy treatment right from the start.

A more detailed look at the STAI-S scores revealed that the ANV group did not score significantly higher on all of the twenty items in this self-report questionnaire. The patients who developed ANV were feeling less at ease, less relaxed, less secure, less steady, less pleasant and less content than the patients who did not develop ANV; and were feeling more jittery, more tense, and more confused than the non-ANV patients before their chemotherapy cycles began. These results must, however, be treated with some caution, as the STAI was not designed to be analysed item by item in this manner.

It is possible to perceive that any attempts to make the patient more at ease, more relaxed, more secure, more steady, more pleasant, less jittery, less tense, and less confused could decrease that patients likelihood of developing ANV and also decrease the posttreatment nausea and vomiting as well. The proposed modes of action for the psychological treatment of ANV generally support this suggestion - as these treatments allow the patient to feel more relaxed, less concerned with their situation, and more in control of themselves. The high levels of state anxiety prior to the first few chemotherapy cycles suggest that an intervention earlier in the process would be more beneficial.

TRAIT ANXIETY

Trait anxiety refers to relatively stable individual differences in anxiety proneness, that is, to differences between people in the tendency to perceive stressful situations as dangerous or threatening and to respond to such situations with elevations in the intensity of their state anxiety. The significance of trait anxiety in relation to the development of anticipatory nausea and vomiting has not previously shown any consistent trend, although whenever there has been a significant relationship it has always been that a higher level of trait anxiety is related to an increased incidence of ANV (Burish & Carey, 1986).

This study has shown that higher levels of trait anxiety are evident in patients who develop ANV as compared to those who do not develop ANV. There appears to be a similar relationship between trait anxiety and the development of ANV as there was with state anxiety; so that significantly higher levels of trait anxiety, as measured using the STAI, were demonstrated before the first three chemotherapy cycles and that significantly higher levels of trait anxiety, as measured using the visual analogue scale, were demonstrated prior to the third and four cycles of chemotherapy. Therefore, these significantly higher levels of trait anxiety were present before most of the ANV patients experienced their first episode of anticipatory nausea or vomiting, and were also present before the highest levels of posttreatment nausea and vomiting were reported. Also, high levels of trait anxiety being reported prior to the first cycle of chemotherapy correlated with a higher level of anticipatory nausea prior to the third and fourth cycles. This implies that patients who see themselves as being more prone to perceiving stressful situations as dangerous or threatening, and especially feeling this way prior to receiving their first cycle of chemotherapy, are more likely to develop ANV. Also, the results show that the level of trait anxiety reported by the ANV patients decreased over time and that this was greater than the decrease observed in the non-ANV patients. This observation also supports the notion of some type of habituation process, so that the patient sees him or herself as more reactive before the first few treatment but decreases this opinion as their treatment progresses.

When the results of the STAI-Trait anxiety questionnaires were analysed in more detail, it was revealed that the ANV group did not score significantly higher on all of the twenty items. The patients who developed ANV saw themselves as being less 'cool, calm and collected', less steady, less secure, and less happy than the patients who did not develop ANV; and the ANV patients saw themselves as being more prone to taking disappointments keenly and being unable to forget them, and more likely to let difficulties pile up to the point where they can not overcome them. Again, these results must be viewed cautiously, as the STAI was not designed to be analysed item by item in this manner.

DEPRESSION

When depression was measured using the Beck Depression Inventory and the 10cm visual analogue scale, both measures revealed that the patients who developed ANV were more depressed before their chemotherapy treatments began than the patients who did not develop ANV. The total BDI scores for the ANV group were significantly higher on the first three chemotherapy cycles, whereas the visual analogue scale had scores significantly higher on cycles two and three. When this is compared to the peaks for posttreatment and pretreatment nausea and vomiting following cycles three and four, it appears that a higher level of depression predisposes a patient to the development of anticipatory nausea and vomiting, as well as more frequent and severe posttreatment nausea and vomiting.

The difference in the level of depression is not merely of statistical significance, but it is of clinical significance as well. The average level of depression reported by the ANV group was in the mild to moderate range, in comparison to an average level of depression for the non-ANV in the none to minimal range. Half of the ANV patients had average depression scores in the mild to moderate range, whereas only one out of the nineteen non-ANV patients had an average score in the mild to moderate range.

One criticism which might be aimed at this finding is the influence which the physiological symptoms in the BDI might have on the scores of the two groups; with the possibility that the ANV patients merely experienced more of physiological symptoms than the non-ANV patients. However, it was shown that there was not a significant

difference between the ANV and non-ANV groups within this subscale of symptoms. However, there were two items in the physiological subscale, loss of appetite and loss of libido, which were significantly higher in the ANV patients. The largest difference was shown to be present in the affective/cognitive items of the BDI - the items which may be seen to be more relevant to the detection of depression in medical populations. The patients who developed ANV recorded significantly higher BDI-Affective/Cognitive subscale scores than the patients who did not develop ANV. Interestingly, there were only two items on the affective/cognitive subscale, pessimism and lack of satisfaction, which were significantly higher in the ANV patients.

Expectancy and the Development of ANV

The patients who experienced ANV displayed higher expectations about experiencing nausea and vomiting as a side effect of their chemotherapy. They were not generally more expectant about the side effects which might accompany their chemotherapy, with the greater expectancy restricted to nausea and vomiting only. There are two possible relationships which may exist between this increased expectancy and the development of ANV. Firstly, these patients were receiving chemotherapy regimens which were more emetogenic than the regimens of those patients who did not develop ANV; so their expectations were not unfounded. However, many of the non-ANV patients who were also receiving very emetogenic regimens, did not have expectations as high as the ANV patients. There is a second relationship which may exist between expectancy and ANV, where those patients who are expecting to experience nausea and vomiting are likely to experience more nausea and vomiting than those patients who do not expect nausea and vomiting, irrespective of the emetogenicity of their chemotherapy.

The relationship between the expectations of the patient and the actual nausea and vomiting which occurs raises an interesting debate about the information which is given to the patient prior to starting their chemotherapy. In this age of 'informed consent' it would not be ethically correct for a patient to start an emetic chemotherapy treatment

without being warned about the possibility of experiencing nausea and vomiting as a side effect of their treatment. However, it may be beneficial for that patient to start their chemotherapy with understated expectations about the probability of them experiencing nausea and vomiting.

Clinical Variables Related to the Development of ANV

There were a number of clinical variables which were found to correlate with the development of ANV. The patients who developed ANV were considerably younger than the patients who did not develop ANV, with five of the six patients with ANV forty or under. This is consistent with much of the previous research in this area, with patients under fifty showing an increased incidence of ANV (Morrow & Dobkin, 1988; Burish & Carey, 1986). The shift from fifty to forty for the increased incidence may just be a result of the age distribution of the subjects in this study or it may indicate that there is a reduced incidence of ANV in patients between forty and fifty with the introduction of the 5-HT_3 receptor antagonists.

There was no relationship between gender and ANV, as similar percentages of the males and females in this study developed ANV. This supports other recent studies, which have also found no relationship between gender and the development of ANV (Boakes et al., 1993). There has been some suggestion that females report more anticipatory symptoms than males (Stefanek et al., 1988) but this was also not supported by this study.

There was also no relationship between ANV and the patients' susceptibility to motion sickness. This result challenges previous studies which have found significant correlations between a patient's susceptibility to motion sickness and their likelihood of developing ANV (Morrow, 1985; Leventhal et al., 1988). The results of this study suggest that patients who are susceptible to motion sickness are not any more likely to develop ANV than patients who do not suffer from motion sickness, with just over half of the ANV group suffering from motion sickness and just under half of the non-ANV

group suffering from motion sickness. On the other hand, Leventhal et al. (1988) reported that 78% of the patients who reported motion sickness also reported developing ANV. Conceivably, it could be that the patients who were susceptible to motion sickness had their nausea and vomiting well controlled using 5-HT_3 receptor antagonists and that this subgroup of patients no longer have an increased risk of developing ANV.

The emetogenicity of the chemotherapy protocol which the patients received was correlated with ANV, so that protocols which were expected to induce more severe and frequent nausea and vomiting were also more likely to result in the patient developing ANV. Similarly, the patients who actually experienced more severe and frequent nausea and vomiting were more likely to develop ANV. The patients who did not develop ANV experienced posttreatment nausea after 56% of their chemotherapy infusions, whereas the patients with ANV experienced posttreatment nausea after 93% of their chemotherapy infusions. Likewise, the non-ANV patients experienced posttreatment vomiting after 23% of their infusions, whereas the ANV patients experienced posttreatment vomiting after 69% of their chemotherapy infusions. In addition, the non-ANV patients rated the posttreatment nausea as 'very mild' on average, while the ANV patients rated their posttreatment nausea as 'moderate' on average. Similarly, the non-ANV patients rated their posttreatment vomiting as less than 'very mild' on average and the patients who developed ANV rated their posttreatment vomiting as 'mild' on average. All of these findings are supported by previous research which has found a positive correlation between posttreatment nausea and vomiting, both frequency and severity, and the development of anticipatory nausea and vomiting (Watson et al., 1992; Kvale et al., 1991; Andrykowski & Redd, 1987; Cohen et al., 1986).

The severity and frequency of posttreatment nausea and vomiting reported in this study can be compared to the prevalence rates of posttreatment nausea and vomiting reported in other studies where 5-HT_3 receptor antagonists have not been used. Leventhal et al. (1986) reported that 86% of the patients in their study experienced posttreatment nausea and 47% experienced posttreatment vomiting, Lindley et al. (1989) reported that 50% of their sample of outpatients experienced posttreatment nausea and 27% experienced posttreatment vomiting, and Lindley and Hirsch (1992)

reported that over 90% of patients receiving high dose cisplatin experience some degree of nausea and/or vomiting. Therefore, the non-ANV patients experienced less nausea and vomiting than would generally be expected without the use of 5-HT_3 receptor antagonists but the patients who did develop ANV experienced more posttreatment nausea and vomiting than would have been expected when 5-HT_3 receptor antagonists were not used. This suggests that the patients who develop ANV are not benefiting as much as other patients from the use of these new and normally highly effective antiemetics. This is not to say that the introduction of 5-HT_3 receptor antagonists has not helped these patients at all, as the severity of anticipatory nausea and vomiting in this study was considerably lower than in studies where 5-HT_3 receptor antagonists have not been used.

The Profile of a Patient Likely to Develop ANV

If it is possible to identify specific clinical, demographic and psychological characteristics which predispose a patient to developing ANV then it should be possible to identify those at risk prior to starting their chemotherapy and provide them with the most effective antiemetics available (currently the 5-HT_3 receptor antagonists), and also give them the option of learning techniques such as progressive muscle relaxation training which have been shown to reduce and/or prevent ANV in the past (Morrow & Dobkin, 1988).

This study has essentially replicated the findings of other researchers, but in a New Zealand environment where the use of the new 5-HT_3 receptor antagonists for the control of chemotherapy-induced nausea and vomiting was widespread. Using relatively quick and easy to administer questionnaires, such as the STAI, BDI and MANE, it has been possible to show significant differences in various characteristics between those patients who developed ANV and those patients who did not develop ANV.

From the results of this study, and by synthesising these results with previous research findings, it is possible to put together a profile of a patient who is at risk of developing ANV. The patient could be male or female, under forty (or maybe fifty)

years of age, and receiving a moderately or highly emetic chemotherapy protocol - especially one containing cisplatin, adriamycin, dacarbazine or high-dose cyclophosphamide.

The psychological profile of the patient who is at risk of developing ANV is of a person who responds to stressful and threatening situations with relatively high levels of anxiety, as supported by other research on the relationship between anxiety and ANV (Andrykowski, 1990). If this person is also suffering from depression at the time of their treatment then they may also have a higher chance of developing ANV, although the relationship between depression and ANV has not been consistently reported. A person with high expectations about the possibility of experiencing nausea and vomiting as a side effect of their chemotherapy could also be more likely to develop ANV. This relationship was not particularly strong in this study, although this relationship between expectancy and ANV has been reported previously (Andrykowski & Redd, 1987).

After receiving the first cycle of chemotherapy it is possible to identify other factors which put the patient at risk of developing ANV. Moderate to severe posttreatment nausea and vomiting after the first cycle of chemotherapy is a good indicator for the development of ANV and also of a continuing problem with emetic control. As already discussed, there is a general consensus about the relationship between posttreatment nausea and vomiting and the development of ANV (Morrow & Dobkin, 1988).

Support for Which Model of Acquisition?

Although it was not the aim of this study to provide support for any of the models of acquisition discussed in the introduction, the results do lend some support to the anxiety model, the autonomic reactivity model and especially strong support is provided for the learned model.

Support for the anxiety model is provided by the observation that there were higher levels of state and trait anxiety in the patients who developed ANV, and that these differences were more apparent before the development of ANV. This is consistent with Andrykowski et al. (1985) who reported higher levels of state anxiety before the

occurrence of ANV. However, it seems paradoxical that the level of anxiety decreases as the incidence of ANV increases.

This same observation may also provide evidence for the autonomic reactivity model, which suggests that people who are more reactive to external and internal stimuli develop conditioned responses more easily than people who are less reactive (Kvale et al., 1991; Ohman & Bohlin, 1973). According to the three-systems model of fear (Hugdahl, 1981; Lang, 1968; Rachman, 1977), anxiety is not an entity, but a set of loosely coupled components of self-reports, autonomic reactivity, and overt avoidance behaviour. Therefore, assuming that trait anxiety and state anxiety (in a stressful situation, such as before chemotherapy) are related to the autonomic reactivity of these patients in some way, then the increased levels of trait and state anxiety in the ANV patients may be consistent with this model.

The majority of the support is provided for the learning model, which applies the laws of classical conditioning to the development of ANV. Firstly, the course of development fits the classical conditioning model, in that for all but one patient, who had experienced nausea and vomiting in response to radiotherapy a few years prior, anticipatory nausea did not develop until after at least two cycles of chemotherapy. Also, the ANV typically started out being very mild but increased over time in most of the patients with ANV. Under the classical conditioning paradigm, it takes a number of presentations of the unconditioned stimulus (chemotherapy) with the conditionable stimulus (any stimuli associated with chemotherapy) for the conditioning to take place and the strength of the conditioned response (ANV) increases with the number of conditioning trials (chemotherapy cycles).

The anticipatory nausea experienced was highly correlated with the level of posttreatment nausea and there were no patients with ANV who had not experienced nausea and/or vomiting prior to the development of ANV; including the patient who had ANV before her first cycle, as she had experienced nausea and vomiting during a previous treatment for her cancer. This fits the classical conditioning model, which states that the conditioned response (ANV) closely resembles the unconditioned

response (posttreatment nausea and vomiting) and that conditioning will never occur in the absence of an unconditioned response (posttreatment nausea and vomiting).

Furthermore, the increased incidence of ANV in those patients who experienced more frequent and severe posttreatment nausea and vomiting provides support for the classical conditioning model in that a more intense unconditioned response (posttreatment nausea and vomiting) enables the conditioned response (ANV) to be established more easily.

The higher incidence of ANV in younger patients can also be explained using the classical conditioning model, in that more novel stimuli are more easily conditioned and it may be that the chemotherapy setting (i.e., hospital, doctors, needles, etc) is likely to contain more novel stimuli for younger patients, who are less likely to have come across these stimuli in the past. Another explanation for the higher incidence in younger patients, which also supports the learned model, is that younger patients may be more likely to receive more emetic chemotherapy protocols (unconditioned stimuli) than older patients and so will be more likely to experience more severe posttreatment nausea and vomiting (unconditioned responses). Under the classical conditioning model, the stronger unconditioned responses (posttreatment nausea and vomiting) make the acquisition of a conditioned response (anticipatory nausea and vomiting) more likely.

The increased anxiety in the ANV patients may also be supportive of the classical conditioning model as it has been suggested that increased anxiety is related to increased conditionability (Jacobsen et al., 1993).

However, there was an observation which challenges the application of the learning model to the development of ANV. There was no perceivable change in the environment in which the patient received his or her chemotherapy but they did not always experience ANV once it had occurred the first time. The chemotherapy was usually given in the same room, by the same people, and usually at around the same time of the day; yet this conditioned response (ANV) did not occur consistently in response to the chemotherapy environment - only occurring before about half of the ANV patients' chemotherapy cycles.

Putting ANV in Perspective

There seems to be little argument about nausea and vomiting being the most traumatic side effect of chemotherapy. It would follow, therefore, that any increase in this nausea and vomiting may have wide ranging implications for the welfare of the patient undergoing chemotherapy. When the nausea and vomiting resulting from chemotherapy becomes too severe, the patient may require hospitalisation, they may require a reduction in the doses of his or her chemotherapy drugs, they may need longer intervals between treatments to recover, or they may even refuse further treatment. Any of these consequences are potentially life-threatening, so any outcome which increases the frequency and/or severity of nausea and vomiting in patients receiving chemotherapy, such as ANV, is of great concern to all those involved.

Anticipatory nausea and vomiting seldom reaches levels which would affect the continued treatment of a patient, with the majority of the ANV patients in this study never having an episode of anticipatory nausea or vomiting above the 'moderate' level. Consequently, ANV is viewed by some cancer specialists as trivial and not of any major concern (Stefanek et al., 1988). However, the patients who develop ANV are noticeably distressed by the whole process of their treatment and any increase in their discomfort is of major concern to them and to many health professionals. So, although there may only be a small percentage of patients who develop ANV it is important that there be some additional support services available for these patients.

In providing these extra services there may be both short and long-term benefits for the patients and the overall financial cost of their treatment. The ability of some psychological treatments to reduce both anticipatory and posttreatment nausea and vomiting may prevent a patient from having to be hospitalised during his or her chemotherapy, may reduce the quantity of expensive antiemetic drugs needed to control his or her nausea and vomiting, may decrease the number of times that patient comes in between treatments for additional consultations, and should generally make their experience with chemotherapy less traumatic. Therefore, the benefits of providing these extra services may greatly outweigh any expense involved.

Limitations of Current Research

The major limitation of this study is that the small number of patients makes any statistical analysis less powerful and open to criticism. However, the small size of the sample has enabled a much more detailed assessment and analysis to be done. Each patient was followed through his or her chemotherapy by the same investigator, enabling the development of a good rapport for the exchange of information - which is difficult when there are a large number of patients in a study. The results which have been obtained here, may therefore be more accurate than in a study where the patient has little contact with the investigator or where they are interviewed by different investigators over the duration of the study.

This study also contained a large proportion of patients receiving moderate to severely emetic chemotherapy regimens. Therefore, any application of these results to a general chemotherapy population is limited. This is not of any great significance, as it is the patients who are receiving these more emetic protocols who are of interest in a study on anticipatory nausea and vomiting. The inclusion of patients receiving mildly emetic regimens is not necessary, and in the future it may be more helpful to state separate prevalence rates for those receiving highly emetic chemotherapy regimens, moderately emetic regimens, and mildly emetic regimens. Also, the sample is fairly representative of the population of chemotherapy patients treated at the Christchurch Hospital Oncology Centre during the time of the study as a high percentage of the new chemotherapy patients treated during that time were included in the analysis.

Another limitation is that this sample of patients consisted only of adult oncology patients, with all patients under eighteen being excluded. Therefore, the actual prevalence of ANV may be higher among all chemotherapy patients, as it has been consistently shown that younger patients experience more anticipatory symptoms than older patients.

The results of the study may also have been affected by the use of progressive muscle relaxation training (PMRT) by two of the patients who did not develop ANV and one patient who did have ANV. It is possible that the use of PMRT may have prevented

these two patients from developing ANV and may have reduced the severity and frequency of ANV in the other patient.

Future Research

There are many questions related to the development of anticipatory nausea and vomiting which remain unanswered and which deserve some attention in future research.

Given that this is one of the first studies on ANV in which 5-HT_3 receptor antagonists have been used in the majority of patients, there is a need for replications of this study to confirm whether the prevalence of ANV has remained constant despite the introduction of these highly effective antiemetics or if there has been a decrease in the prevalence which the small number of patients in this study was unable to detect. Confirmation is also needed for the observation that the severity of anticipatory nausea and vomiting has decreased with the introduction of these new antiemetics.

There needs to be more research into the relationship between anxiety and ANV, especially with an aim towards finding ways to predict the development of ANV by measuring anxiety levels before starting chemotherapy. There have been no studies to date which have reported a decrease in anxiety over time in patients with ANV as was shown in this study, so more research is needed to determine if this is a consistent phenomenon.

The relationship between expectancy and ANV is one which has not been examined in great detail as yet. Research into the effects of providing patients with different expectations, irrespective of the emetogenicity of their chemotherapy, should help to clarify the relationship between a patients expectations of experiencing nausea and vomiting and the actual occurrence of nausea and vomiting.

The low prevalence of ANV in patients between forty and fifty suggests that there has been a shift in the age of susceptibility from under fifty to under forty. More research in settings where 5-HT_3 receptor antagonists are used would be helpful in determining the accuracy of this hypothesis.

This study's inability to confirm that patients who are susceptible to motion sickness are more likely to develop ANV may indicate that these patients are no longer at greater risk of developing ANV with the introduction of the 5-HT_3 receptor antagonists. Replications of this study should confirm or deny this hypothesis.

Most importantly, there is a great deal which can be done to reduce or prevent ANV using various psychological treatment methods, but there is no current consensus about which treatment modalities work most effectively and efficiently. Therefore, there is a need for research which compares the effectiveness of various treatment methods and the cost involved in providing these services, both with patients who already have ANV and patients who do not have ANV but who are at risk of developing ANV.

Chapter V

CONCLUSIONS

The main conclusion to come from this study is that the prevalence of anticipatory nausea and vomiting has not been dramatically reduced with the introduction of 5-HT_3 receptor antagonists as the mainstay of antiemetic treatment. Indeed, it appears that ANV still occurs in approximately one quarter of patients receiving chemotherapy. However, there is a strong indication that the severity of the anticipatory nausea and vomiting has been reduced substantially.

Another major finding is the relationship between state anxiety, trait anxiety and the development of ANV. Patients who are more anxious at the start of their chemotherapy are more likely to develop nausea and vomiting, and this is true for both state and trait anxiety. Similarly, patients who are more depressed at the start of their treatment are also more likely to develop ANV. It seems that the difference between the ANV patients and non-ANV patients decreases over time with respect to anxiety and depression levels, further implicating the importance of the first few chemotherapy cycles in the subsequent development of ANV.

The patients' expectations about the occurrence of nausea and vomiting as a side effect of their chemotherapy also seem to influence the development of ANV. Patients who are more expectant of nausea and vomiting are more likely to develop ANV and also more likely to experience more severe posttreatment nausea and vomiting.

Younger patients have an increased risk of developing ANV and it seems that patients under forty are particularly susceptible. More emetogenic chemotherapy protocols also put a patient at risk of developing ANV, as well as patients who experience more severe posttreatment nausea and vomiting.

The results tend to provide the most support for the learned model of acquisition, following the classical conditioning model's guidelines for the course of development; including the relationship between the conditioned response (ANV) and unconditioned response (posttreatment nausea and vomiting), the intensity of unconditioned response (posttreatment nausea and vomiting) and ease of acquisition, anxiety and conditionability, and novel stimuli being more easily conditioned.

Finally, it does seem possible to identify patients at risk of developing ANV before, or soon after, they start their chemotherapy and providing additional support services for

these patients may considerably reduce the likelihood of them developing ANV during their chemotherapy. Furthermore, this extra support may produce other benefits which greatly outweigh the cost of providing these services.

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APPENDICES

APPENDIX 1.

Chemotherapy Emetogenicity Questionnaire

Chemotherapy Drug Toxicity:

This questionnaire has been designed to assess the perceived toxicity (emetogenicity) of the chemotherapy drugs currently being used for the treatment of cancer. Estimates of how frequent and severe the episodes of vomiting are with these drugs is required. Each drug is being assessed individually despite the fact that they are often given in combination with each other. Any comments about specific drugs or any general comments you wish to make can be written in the available space below. The results from this questionnaire will be used in the Anticipatory Nausea and Vomiting study which is currently being conducted. It would be appreciated if you could complete this questionnaire and return it to Robert McNeill in Clinic 4 of the Oncology Department.

Comments:

Position held: Doctor / Nurse / Radiographer (Circle one)
How long have you worked in oncology?: _____Years _____Months

Please circle the appropriate numbers which you think correspond to both the frequency and severity of vomiting elicited by the following chemotherapy drugs. If you are unsure about a drug leave it blank.

	Frequency:					Severity:		
	0=Never induces vomiting.					1=Mild		
	1=Rarely induces vomiting.					2=Moderate		
	2=Induces vomiting about half the time.					3=Severe		
	3=Frequently induces vomiting.							
	4=Always induces vomiting.							
5-Fluorouracil	0	1	2	3	4	1	2	3
Folinic Acid	0	1	2	3	4	1	2	3
Adriamycin	0	1	2	3	4	1	2	3
BCNU	0	1	2	3	4	1	2	3
Cyclophosphamide	0	1	2	3	4	1	2	3
Melphalan	0	1	2	3	4	1	2	3
Bleomycin	0	1	2	3	4	1	2	3
Vinblastine	0	1	2	3	4	1	2	3
Dacarbazine (DTIC)	0	1	2	3	4	1	2	3
Cisplatin	0	1	2	3	4	1	2	3
Etoposide	0	1	2	3	4	1	2	3
Prednisone	0	1	2	3	4	1	2	3
Carboplatin (JM8)	0	1	2	3	4	1	2	3
Lomustine (CCNU)	0	1	2	3	4	1	2	3
Chlorambucil	0	1	2	3	4	1	2	3
Procarbazine	0	1	2	3	4	1	2	3
Methotrexate	0	1	2	3	4	1	2	3
Vincristine	0	1	2	3	4	1	2	3
Actinomycin D	0	1	2	3	4	1	2	3
Ifosfamide	0	1	2	3	4	1	2	3
Mesna	0	1	2	3	4	1	2	3
Mustine	0	1	2	3	4	1	2	3
Mitozantrone	0	1	2	3	4	1	2	3

Thankyou.

APPENDIX 2.

Information Sheet

Anticipatory Nausea and Vomiting Associated with Cancer Chemotherapy.

Information Sheet

Title:

Anticipatory nausea and vomiting in cancer chemotherapy patients: the effect of different antiemetics on prevalence.

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Aim of Project:

There are two aims of this project: Firstly, to determine the efficacy of ondansetron in the prevention and treatment of anticipatory nausea and vomiting; and secondly, to compare the frequency of anticipatory nausea and vomiting in patients who have good or bad control of their sickness.

Background:

The nausea and vomiting that accompanies chemotherapy occurs in two different contexts; before the chemotherapy drugs are administered (anticipatory nausea and vomiting, ANV), and during or after the drugs have been administered (posttreatment nausea and vomiting, PNV). Various things seem to make people more likely to experience nausea and vomiting, including being younger, higher doses of chemotherapy, the kind of drugs given, and also how they are feeling and their life situation. The recent introduction of ondansetron antiemetic therapy has produced a lot of studies which indicate that this new drug is very effective in reducing posttreatment nausea and vomiting without many of the side effects that accompany most other antiemetics. However, it has not yet been established whether ondansetron affects anticipatory nausea and vomiting.

Patients Eligible to Participate:

Patients must be older than 17 years, be receiving intravenous chemotherapy, have had no other chemotherapy in the past and be able to give consent.

Patients are not eligible if they have pre-existing nausea and/or vomiting due to brain metastases or gastrointestinal involvement by cancer.

Outline of Study:

After deciding they wish to participate and signing the informed consent form the patients will be divided into two antiemetic groups depending on whether their doctor prescribes metoclopramide (maxolon) or ondansetron for their first course of chemotherapy. Patients who receive maxolon for their first treatment and experience

severe posttreatment nausea and vomiting (>5 emetic incidences/day) will usually be transferred to ondansetron for their next chemotherapy treatment. Some patients may also be prescribed dexamethasone as well as ondansetron if their nausea and vomiting is severe. Patients will be followed for at least four cycles of chemotherapy. Some patients may develop anticipatory nausea and vomiting. If this occurs they will be offered a relaxation therapy called progressive muscle relaxation training (PRT) which may help the patient with his/her nausea and vomiting.

The patients in the study will be interviewed before their first chemotherapy treatment and with each subsequent course, to check things which might influence their nausea and vomiting. In addition, patients will be asked to complete an assessment of their nausea and vomiting after the cycle is completed.

Progressive Muscle Relaxation Training:

Patients who experience anticipatory nausea and vomiting will be offered training in progressive muscle relaxation. In addition, other patients will be able to have this training if they wish to. This procedure consists of learning to tense and then relax various muscle groups throughout the body, while at the same time paying very close attention to the feelings associated with both tension and relaxation. In addition to focusing on tension and relaxation in the various muscle groups, it helps the patient to learn to recognise tension as it occurs in various situations. The procedure has two basic objectives: first, to help the patient become aware of tension levels before they are so high that they cause problems or discomfort; and second, to be able to reduce tension completely and on their own. Progressive relaxation training has been used to successfully treat anticipatory nausea and vomiting in the past and has also been used to treat a variety of other problems such as insomnia and anxiety.

Inconveniences:

The interviews should take no longer than 20 minutes, except the first interview which may take up to 30 minutes. It will take approximately 5 minutes to complete the nausea and vomiting assessment questionnaire after each cycle is completed. Those who attend the progressive relaxation training sessions will find the first session takes about 30 minutes but the subsequent sessions take only about 20 minutes.

Benefits:

Patients will benefit from close attention to their nausea and vomiting, and those who develop anticipatory nausea and vomiting will be able to have progressive relaxation training, not formerly available in the Oncology Department.

Confidentiality:

Patients' names will not appear on any data sheets, interview sheets or in any publications - all patients will be numbered and this number will appear in place of their name. We hope the study results will be able to be analysed and presented as a paper or published.

Compensation:

Patients will be covered for any injuries associated with participating in this study by the Department of Health.

Informed Consent:

You will be told about this study and given this information sheet at the same time that you are learning about the need for chemotherapy for your cancer. You will be given the opportunity to discuss both your chemotherapy and this study with a doctor or other person of your choice and to have all your questions answered by your doctor. Unless the patient objects, their general practitioner will be notified about their chemotherapy, its likely side effects and their participation in this study.

You are free to decline to participate, without giving reasons, and to withdraw your consent at any time. In either case, you will receive the best antiemetic medication, and

will not prejudice your ongoing medical care. Furthermore, your doctor may recommend you withdraw from the trial if it is no longer in your best interest to continue. If you agree to participate you need to sign the attached consent form.

APPENDIX 3.

Progressive Muscle Relaxation Training Patient Results

Table 28 shows that this patient 017 never developed anticipatory nausea and vomiting. This patient received training before her first two cycles and then stopped PMRT due to a neck injury which made the exercises uncomfortable. Figure 21 shows that the worst posttreatment nausea that she experienced was 'moderate' following cycle four (her father had died just before receiving this cycle of chemotherapy).

Table 28.
Patient 017

	Cycle					
	1	**2**	**3**	**4**	**5**	**6**
PMRT	Yes	Yes	No	No	No	No
STAI-S	53	40	40	29	28	25
STAI-T	39	35	35	30	25	21
State Anxiety	0	8	10	6	8	2
Trait Anxiety	9	43	21	6	15	29
BDI-Total	12	5	11	6	7	5
BDI-PS	8	3	8	5	5	3
BDI-A/CS	4	2	3	1	2	2
Depression	0	6	26	10	8	4
PN	2	2	2	3	0	1
PV	2	2	2	1	1	1
AN	0	0	0	0	0	0
AV	0	0	0	0	0	0

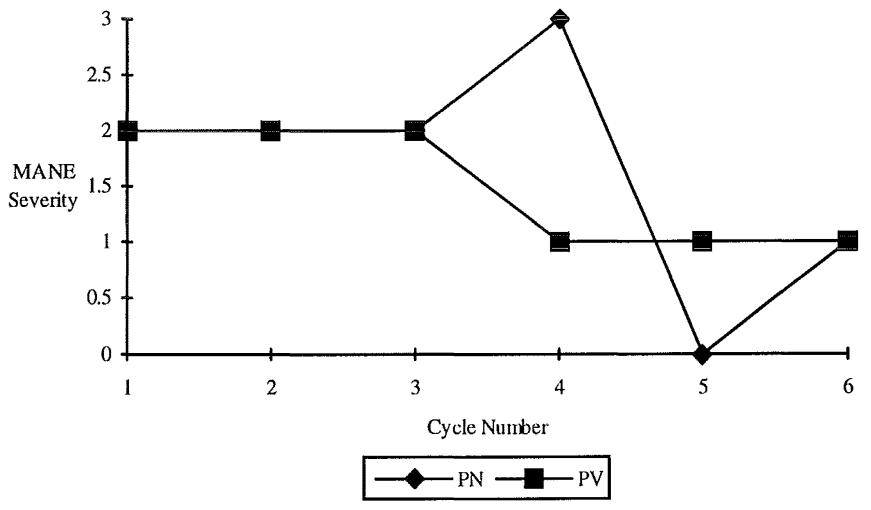

Figure 20. *Patient 017 - Posttreatment Nausea and Vomiting*

Patient 007 received progressive muscle relaxation training before starting her fourth cycle of chemotherapy and was shown through the procedure before three consecutive cycles. Figure 22 and Table 29 show that this patient experienced 'severe' anticipatory nausea prior to receiving her fourth cycle of chemotherapy and after that there were no anticipatory symptoms reported, which coincided with the introduction of PMRT.

Table 29.
Patient 007

	Cycle											
	1a	**1b**	**2a**	**2b**	**3a**	**3b**	**4a**	**4b**	**5a**	**5b**	**6a**	**6b**
PMRT	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No
STAI-S	60	29	35	20	49	33	22	23	25	26	21	32
STAI-T	60	51	62	45	40	56	32	37	27	25	25	25
State Anxiety mm	82	11	21	0	2	31	9	3	12	14	0	2
Trait Anxiety mm	69	48	59	61	43	66	33	34	46	32	19	34
BDI-Total	22	9	19	12	3	14	2	3	0	0	0	3
BDI-PS	12	6	7	3	0	4	0	1	0	0	0	3
BDI-A/CS	10	3	12	9	3	10	2	2	0	0	0	3
Depression mm	17	12	26	0	2	2	0	2	0	1	0	2
PN	5	5	2	5	6	5	4	4	0	3	5	2
PV	5	2	0	0	5	0	0	0	0	0	0	0
AN	0	0	0	2	3	3	4	0	0	0	0	0
AV	0	0	0	0	0	0	0	0	0	0	0	0

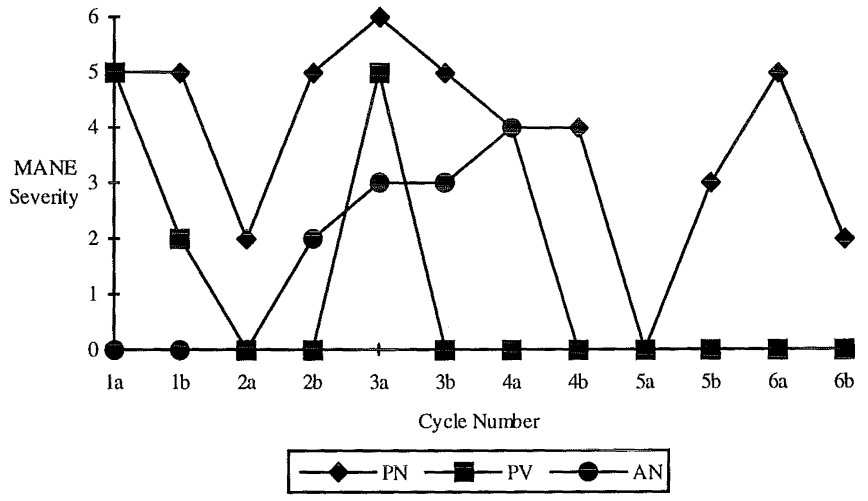

Figure 21. *Patient 007 - Nausea and Vomiting*

Patient 020 was shown the PMRT procedure before his first two chemotherapy cycles. Figure 23 and Table 30 show that this patient never developed any anticipatory symptoms and never experienced any posttreatment nausea above the 'moderate' level, with no posttreatment vomiting at all.

Table 30.
Patient 020

	Cycle							
	1a	**1b**	**2a**	**2b**	**3a**	**3b**	**4a**	**4b**
PMRT	Yes	Yes	No	No	No	No	No	No
STAI-S	40	37	30	28	32	35	33	29
STAI-T	33	28	28	30	28	28	28	29
State Anxiety mm	48	19	2	6	8	10	3	5
Trait Anxiety mm	24	0	4	0	2	10	3	2
BDI-Total	2	2	3	2	3	3	4	2
BDI-PS	2	2	3	2	3	2	3	1
BDI-A/CS	0	0	0	0	0	1	1	1
Depression mm	4	0	3	0	3	0	12	5
PN	1	2	3	3	0	0	1	2
PV	0	0	0	0	0	0	0	0
AN	0	0	0	0	0	0	0	0
AV	0	0	0	0	0	0	0	0

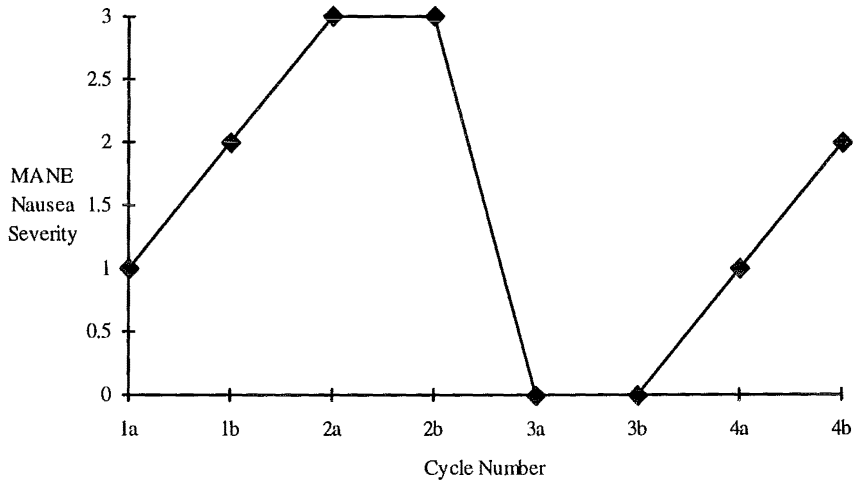

Figure 22. *Patient 020 - Posttreatment Nausea*

APPENDIX 4.

Side Effect Expectancy Questionnaire

Patient No.:_____ Date:_____

Here is a list of side effects that some patients have with some chemotherapies. For each side effect, please circle one number that best indicates your feelings.

Nausea	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Vomiting	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Feeling tired	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Hair loss	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Nervousness	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Change in taste or appetite	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Weight loss	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Weight gain	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Skin itching	I am certain I will not have this	1	2	3	4	5	I am certain I will have this

Pain	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Weakness	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Diarrhoea	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Sleep problems	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Chills	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Problems with sex	I am certain I will not have this	1	2	3	4	5	I am certain I will have this
Constipation	I am certain I will not have this	1	2	3	4	5	I am certain I will have this

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Do you suffer from motion sickness (Car, Boat, Plane, Train etc.) ?

YES / NO

Comments:

APPENDIX 5.

State Anxiety, Trait Anxiety, and Depression 10cm Visual Analogue Scales

Patient No.:_____ Date:_____

Are you feeling anxious at the moment?

Not at all Anxious ——————————————— Very Anxious

Are you an anxious person generally?

Not at all Anxious ——————————————— Very Anxious

Are you feeling depressed?

Not at all Depressed ——————————————— Very Depressed

APPENDIX 6.

Chemotherapy Protocols

Table 31.

Chemotherapy Protocols

Patient	Chemotherapy Protocol
1	Day 1: Adriamycin 50mg IV; Day 2: Adriamycin 60mg IV
2	Day 1: Cyclophosphamide 1000mg IV, Methotrexate 70mg IV, 5-FU 1000mg IV
3	Day 1: Cyclophosphamide 1500mg IV, Etoposide 200mg IV, Vincristine 2mg IV; Day 2: Etoposide 200mg IV; Days 3-6: Prednisone 60mg PO
4	Day 1: Cyclophosphamide 10mg/kg IV, Adriamycin 1mg/kg IV; Days 2-5: Prednisone 1mg/kg PO
5	Day 1: Cyclophosphamide 750mg/m² IV, Adriamycin 50mg/m² IV, Vincristine 1.4mg/m² IV; Days 2-5: Prednisone 40mg PO
6	Day 1: Cyclophosphamide 750mg/m² IV, Adriamycin 50mg/m² IV, Vincristine 1.4mg/m² IV, Methotrexate 12.5mg IT; Days 2-5: Prednisone 40mg PO
7	Day 1: Adriamycin 25mg/m² IV, Bleomycin 10mg/m² IV, Vinblastine 6mg/m² IV, Dacarbazine 375mg/m² IV
8	Day 1: Carboplatin 670mg IV
9	Day 1: Carboplatin 650mg IV
10	Cycle 1: Daily 5-FU* 450mg/m² IV for 5 days, then six months of : Weekly 5-FU 450mg/m² IV + Fortnightly Levamisole 50mg PO
11	Day 1: Cyclophosphamide 1000mg IV, Methotrexate 70mg IV, 5-FU 1000mg IV
12	Day 1: Cyclophosphamide 1000mg IV
13	Cycle 1: Daily 5-FU 450mg/m² IV for 5 days, then six months of : Weekly 5-FU* 450mg/m² IV + Fortnightly Levamisole 50mg PO
14	Day 1-2: Cisplatin 50mg/m² IV; Days 1-3: Etoposide 120mg/m² IV; Day 3: Bleomycin 30mg IV
15	Day 1-2: Cisplatin 50mg/m² IV; Days 1-3: Etoposide 120mg/m² IV; Day 3: Bleomycin 30mg IV
16	Cycle 1: Daily 5-FU 450mg/m² IV for 5 days, then six months of : Weekly 5-FU* 450mg/m² IV + Fortnightly Levamisole 50mg PO
17	Day 1: Cyclophosphamide 600mg/m² IV, Methotrexate 40mg/m² IV, 5-FU 600mg/m²IV
18	Day 1-2: Cisplatin 50mg/m² IV; Days 1-3: Etoposide 120mg/m² IV; Day 3: Bleomycin 30mg IV
19	Chlorambucil 6mg/m² PO, Vinblastine 6mg/m² IV, Procarbazine 100mg/m² PO, Prednisone 40mg/m² PO
20	Day 1: Adriamycin 25mg/m² IV, Bleomycin 10mg/m² IV, Vinblastine 6mg/m² IV, Dacarbazine 375mg/m² IV
21	Day 1-2: Cisplatin 50mg/m² IV; Days 1-3: Etoposide 120mg/m² IV; Day 3: Bleomycin 30mg IV
22	Day 1: Cyclophosphamide 1000mg IV
23	Day 1: Adriamycin 25mg/m² IV, Bleomycin 10mg/m² IV, Vinblastine 6mg/m² IV, Dacarbazine 375mg/m² IV
24	Day 1: Cyclophosphamide 750mg/m² IV, Adriamycin 50mg/m² IV, Vincristine 1.4mg/m² IV, Methotrexate 12.5mg IT; Days 2-5: Prednisone 40mg PO
25	Cycle 1: Daily 5-FU 450mg/m² IV for 5 days, then six months of : Weekly 5-FU* 450mg/m² IV + Fortnightly Levamisole 50mg PO
26	Day 1: Cyclophosphamide 600mg/m² IV, Methotrexate 40mg/m² IV, 5-FU 600mg/m² IV